2023 WINTER CONFERENCE ON BRAIN RESEARCH

55TH ANNUAL WINTER CONFERENCE ON BRAIN RESEARCH

2023 Program Book

SNOWBIRD RESORT
SNOWBIRD, UTAH
JANUARY 20 - 25, 2023

WWW.WINTERBRAIN.ORG

Welcome to WCBR!

Welcome to the 55th Meeting of the Winter Conference on Brain Research, held this year at Snowbird, Utah. As is the tradition at WCBR, the Executive Committee, Board of Directors, Program Committee, and panel and poster presenters have all contributed to our outstanding program of basic and applied research, clinical insights, professional development, and science education. We can explore our agenda in the conference app, website schedule, and pocket guide to the meeting.

As this year's registration numbers push toward record heights, we are reminded of the importance and excitement around face-to-face opportunities to exchange ideas and innovate together. As the COVID-19 virus continues to evolve, however, we respect all attendees who wish to mask-up for safety and we know that the meeting organizers might need to request masking for everyone if local conditions warrant such precautions. In many ways, the pandemic has taught us to acknowledge more fully the individual needs of our friends and colleagues, a lesson we have worked to apply also to recognizing, valuing, and celebrating all sorts of diversity in our scientific community. Everyone who shares the goal of mutual respect and productive dialogue is welcomed to attend annually and encouraged to engage fully at WCBR.

The scientific program kicks off with a plenary presentation on Saturday morning by Dr. Elizabeth Phelps, Pershing Square Professor of Human Neuroscience at Harvard University. Her work on emotion processing in the context of learning, memory, and decision-making has been well-received for decades. In keeping with WCBR's recent enhancements related to diversity and inclusion, Dr. Phelps will focus her remarks on the neural systems mediating the processing of social groups defined by race. On Monday evening, she will be joined by Drs. Laura O'Dell and Stefano Cataldi to consider the implications of her work for inclusion and belonging among the next generation of neuroscientists and informed citizens of our world.

More than 80 panels, 160 posters, two short courses, two professional development sessions, and a diversity and inclusion power hour round out the exciting and energizing program of WCBR 2023. In support of budding scientists, WCBR attendees are also invited to join our virtual outreach program to make presentations to K-12 classrooms and answer career-related questions. Tuesday is especially packed with the ski race, mountain lunch, business meeting, and special poster session during which top-ranked posters are judged for WCBR

Welcome to WCBR!

awards. Also be on the look-out this week for our travel fellows (white ribbons) and first-time attendees (yellow badges) to congratulate and welcome them.

At the 50th Meeting in 2017, WCBR launched the annual Pioneer Awards, and we applaud the lifetime achievements of two outstanding scientists this year. Dr. Phil Skolnick of Opiant Pharmaceuticals will highlight his career spanning academic, government, and industry positions, with focus on the opioid epidemic, the rising number of synthetic opioid overdoses, and the pressing need for overdose reversal agents. Dr. Marisela Morales of the National Institute on Drug Abuse will be joined by three of her former trainees to lead us on her path toward discovering the diversity of neuron types and neurotransmitter co-release strategies that regulate reward, aversion, and other behaviors in the ventral tegmental area. Both pioneers are faithful WCBR attendees, with past and present leadership roles. They are also passionate supporters of their academic and biological offspring who frequently attend and enhance WCBR.

The future of WCBR depends on you. Keep coming to share your science, celebrate your triumphs, honor our highly successful colleagues, and welcome both novice and senior scientists and practitioners to our community. Nominate yourselves or your colleagues for election to the Board of Directors. Share yourselves and your many identities with the friends you make at the meeting. Enjoy this invigorating combination of outstanding scientific exchange and exciting winter activities. Thank you!

Kyle J. Frantz, Conference Chair
55th Winter Conference on Brain Research
Snowbird Utah, January 20 – January 25, 2023

CONTENTS

Registration

WCBR Registration Desk and Message Center are located in the Cliff Lodge Ballroom Lobby at Snowbird Resort.

The Registration Desk hours are as follows:

Friday, January 20, 2023	12:00 p.m. – 7:00 p.m.
Saturday, January 21, 2023	7:00 a.m. – 12:00 p.m., 2:00 p.m. - 7:30 p.m.
Sunday, January 22, 2023	7:00 a.m. – 11:30 a.m., 2:30 p.m. - 7:30 p.m.
Monday, January 23, 2023	7:00 a.m. – 11:30 a.m., 2:00 p.m. - 7:30 p.m.
Tuesday, January 24, 2023	7:00 a.m. – 10:00 a.m., 2:00 p.m. - 7:00 p.m.
Wednesday, January 25, 2023	7:00 a.m. – 10:00 a.m., 3:00 p.m. - 6:00 p.m.

Pick up your badge at the WCBR Registration Desk in the Cliff Lodge Ballroom Lobby at Snowbird Resort. If you have purchased guest meal tickets, these will also be available at registration.

Exhibits and Poster Sessions

Exhibits and Poster Sessions are in Ballrooms 2 & 3. Light refreshments are provided from 3:30 p.m. – 4:30 p.m., Saturday, January 21 through Tuesday, January 24. Exhibitor setup is Saturday, January 21, from 1:00 p.m. – 3:00 p.m. All exhibitors should have their materials removed by 10:00 p.m. on Tuesday, January 24.

POSTER SESSION I, SATURDAY, JANUARY 21
Posters can be set up after 1:00 p.m. on Saturday.

Posters will be available for viewing from 3:00 p.m. – 7:00 p.m. on Saturday. Presenters will be at their posters from 3:30 p.m. – 4:30 p.m. Posters must be removed by 8:30 p.m. on Saturday.

Continued on next page.

Exhibits and Poster Sessions

POSTER SESSION 2, SUNDAY, JANUARY 22
Posters must be set up between 8:00 a.m. – 11:30 a.m. on Sunday.

Posters will be available for viewing from 12:00 p.m. – 7:00 p.m. on Sunday. Presenters will be at their posters from 3:30 p.m. – 4:30 p.m. Posters must be removed by 8:30 p.m. on Sunday.

POSTER SESSION 3, MONDAY, JANUARY 23
Posters must be set up between 8:00 a.m. – 11:30 a.m. on Monday.

Posters will be available for viewing from 12:00 p.m. – 7:00 p.m. on Monday. Presenters will be at their posters from 3:30 p.m. – 4:30 p.m. Posters must be removed by 8:30 p.m. on Monday.

POSTER SESSION 4, TUESDAY, JANUARY 24
Posters must be set up between 8:00 a.m. – 11:30 a.m. on Tuesday.

This is a special session displaying the highest-ranked posters by young investigators. Award certificates will be presented to the best posters. Presenters will be at their posters from 3:30 p.m. – 4:30 p.m. and return for the special session from 7:30 p.m. – 9:30 p.m. Posters must be removed by 10:00 p.m. on Tuesday. Please refer to pages 36-53 for a listing of poster sessions.

Breakfast

Breakfast is served to all conference delegates during the keynote presentation on Saturday, January 21 from 7:00 a.m. – 8:30 a.m. in the Cliff Lodge Ballroom.

Sunday through Wednesday breakfast will be available at restaurants around Snowbird. Breakfast vouchers will be distributed at registration and hold a maximum value of $25.00 each for breakfast. Vouchers can be used at the following locations:

- SeventyOne* in Cliff Lodge
- The Atrium* in Cliff Lodge
- The Forklift in Snowbird Center
- General Gritts in Snowbird Center
- Baked & Brewed at The Bird in Snowbird Center

**SeventyOne and The Atrium will open at 6:30 AM to accommodate early risers.*

Continuing Medical Education

SATISFACTORY COMPLETION

Learners must complete an evaluation form to receive a certificate of completion. Your chosen sessions must be attended in their entirety. Partial credit of individual sessions is not available. If you are seeking continuing education credit for a specialty not listed below, it is your responsibility to contact your licensing/certification board to determine course eligibility for your licensing/certification requirement.

JOINTLY ACCREDITED PROVIDER™
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PHYSICIANS

In support of improving patient care, this activity has been planned and implemented by Amedco LLC and the Winter Conference on Brain Research (WCBR).Amedco LLC is jointly accredited by the Accreditation Council for Continuing Medical Education (ACCME), the Accreditation Council for Pharmacy Education (ACPE), and the American Nurses Credentialing Center (ANCC), to provide continuing education for the healthcare team.

Credit Designation Statement – Amedco LLC designates this live activity for a maximum of 28.5 AMA PRA Category 1 Credits™ for physicians. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

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Each year WCBR offers travel fellowships to young investigators to encourage outstanding new investigator participation in the meeting. This has been a very successful program. Unrestricted donations to the fellowship program can be made at any value.

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2023 Fellowship Awardees

Yocasta Alvarez-Bagnarol
Lillian Brady – *Science Advances Travel Fellow*
Svetlana Bryant
James Burkett
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Thank you to the individuals and organizations that generously support the Travel Fellowship Program. The gift you make is used exclusively to introduce young neuroscientists to the WCBR meeting.

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Craig Berridge
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EXHIBITORS

Thank you to the Winter Conference on Brain Research exhibitors.

INNOVATIONS FOR SUBSTANCE USE DISORDERS
Johns Hopkins Carey Business School Executive Education
100 International Drive
Baltimore, MD 21202
Contact: Patrick H. Finan, PhD
tpx4xe@uvahealth.org

MARINUS PHARMACEUTICALS
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CODE OF CONDUCT

1. Introduction

The Winter Conference on Brain Research (WCBR) is dedicated to providing a safe, productive and discrimination-free experience for all participants during the Annual Meeting regardless of race, color, national origin, religion, creed, age, sex (including pregnancy), gender, gender identity, physical or mental disability, perceived disability, ancestry, marital status, genetic information, sexual orientation, citizenship, past, current or prospective service in the uniformed services, or any other basis protected by federal, state or local laws. WCBR does not tolerate discrimination or any form of harassment and is committed to enforcing this Code of Conduct Policy. As a professional society, the WCBR is committed to providing an atmosphere that encourages the free expression and exchange of scientific and educational ideas. Furthermore, WCBR upholds the philosophy of equality of opportunity for, and treatment of, all meeting participants, including but not limited to, attendees, guests, speakers, exhibitors, contractors, staff, and volunteers at all venues and events, including all ancillary and unofficial social events held in conjunction with the Annual Meeting (collectively “Annual Meeting”).

2. Scope of Code of Conduct

WCBR seeks to create a diverse, inclusive and respectful environment for the exchange of scientific information.

WCBR requires compliance with this Policy by all meeting participants throughout the period of the Annual Meeting, whether in public or private facilities. This policy is an expression of WCBR’s values and commitment to a safe and productive experience for all participants at the Annual Meeting. This policy is not an acknowledgement, admission, or description of WCBR’s legal obligations with respect to any of the subject matters addressed herein, nor does it create any such legal obligations on WCBR, its Board Members, and committee members.

3. Prohibited Conduct

Prohibited conduct at the WCBR Annual Meetings include, but is not limited to:

- harassment and discrimination based on race, color, national origin, religion, creed, age, sex (including pregnancy), gender, gender identity, physical or mental disability, perceived disability, ancestry, marital status, genetic information, sexual orientation, citizenship, past, current or prospective service in the uniformed services, or any other basis protected by federal, state or local laws;

CODE OF CONDUCT CONTINUED

- demeaning comments or harassment about a person's professional status, qualifications, or affiliations;
- sexual harrassment, as defined in Section 4;
- abusive conduct that has the purpose or effect of unreasonably interfering with another person's ability to benefit from and enjoy or participate in the Annual Meeting;
- undue or excessive interruption of any event, speaker, or session; and
- violence or threats of violence or physical harm.

4. Harassment Defined

Prohibited harassment includes any conduct that creates an intimidating, offensive, or hostile environment whether that conduct be verbal, physical, or visual. Harassment can take many forms and includes, but is not limited to, the following: slurs, epithets, derogatory comments, insults, degrading or obscene words, jokes, demeaning statements, offensive gestures, or displaying derogatory or demeaning pictures, photos, drawings, or cartoons based upon an individual’s race, color, national origin, religion, creed, age, sex, pregnancy, gender, gender identity, physical or mental disability, perceived disability, ancestry, marital status, genetic information, sexual orientation, citizenship, past, current or prospective service in the uniformed services, or any other basis protected by federal, state or local laws. Sexual harassment includes unwanted sexual attention including expressions of romantic or sexual interest that are unwelcome, unreciprocated, and/or offensive to the target; examples include unwanted touching, hugging, stroking, and persistent requests for dates or sexual behavior despite discouragement. Sexual harassment also includes gender harassment which includes verbal and nonverbal behaviors that convey insulting, hostile, and degrading attitudes about members of one gender as well as crude harassment.

Sexually harassing conduct can be by a person of either the same or other sex. Conduct that begins as consensual in nature may become harassment if one party withdraws his or her consent. Sexual or other harassment prohibited by this policy is unacceptable and will not be tolerated.

The above list of prohibited behaviors is not a complete rendering of what may be deemed sexual or other harassment prohibited by this policy. It is impossible to define every action or word that could be interpreted as harassment or discrimination. However, WCBR has a “zero tolerance” policy toward discrimination and all forms of harassment. WCBR reserves the right to discipline meeting participants who engage in any inappropriate conduct, even if it is not specifically referred to or defined in this Code of Conduct, or is not legally actionable as sexual or any other form of harassment.

CODE OF CONDUCT CONTINUED

5. Filing a Formal Complaint

If you feel you have been subject to or have witnessed a violation of this Code of Conduct, a formal complaint can be filed with an authorized representative from our meeting management company, Parthenon Management Group, LLC. This individual can be contacted through the registration desk, or if after the Annual Meeting, at 615-324-2365. No participant will be retaliated against for making a good faith claim of harassment or discrimination, for opposing harassment or discrimination, or for participating in, or cooperating with, the investigation of a complaint. A designated member of the Parthenon team will gather information and put together a summary report, which will then be forwarded to the Conduct Subcommittee of the Executive Board of WCBR for a decision. If the decision of the Subcommittee is contested, it can be appealed to the full Executive Board. The decision following appeal is final and not subject to further appeal. We will strive to keep the identity of the complainant and any witnesses, as well as the accused individual, confidential throughout this process. All participants of the Annual Meeting are bound by the decisions of the Conduct Subcommittee of the Executive Board. If it is determined that an individual has engaged in conduct constituting harassment or discrimination, discipline may be imposed, up to and including exclusion from participating in the WCBR Annual Meeting, and/or future meetings.

Code of Conduct Attestation

The WCBR Annual Meeting is committed to supporting discovery and scientific dialogue, and providing an atmosphere that is safe, respectful and welcoming to all those present in order to encourage the free expression and exchange of scientific and educational ideas. This commitment applies to the WCBR Annual Meeting, at all venues and events, including all ancillary and unofficial social events held in conjunction with the Annual Meeting (collectively “Annual Meeting”) and anyone present, including but not limited to, attendees, guests, speakers, exhibitors, contractors, staff, and volunteers.

To that end, the WCBR Annual Meeting strictly prohibits and does not tolerate unlawful harassment or discrimination on the basis of race, color, religion, creed, national origin, ancestry, sex (including pregnancy), sexual orientation, gender (including nonconformity and status as a transgender or transsexual individual), gender identity, age, physical or mental disability, perceived disability, citizenship, marital status, genetic information, past, current or prospective service in the uniformed services, or any other basis recognized by applicable federal, state, or local laws. WCBR upholds the philosophy of equality of opportunity for, and treatment of, all individuals present at the Annual

CODE OF CONDUCT CONTINUED

Meeting and thus, does not tolerate any form of discrimination, harassment, and/or retaliation. We expect all those present at the Annual Meeting of the WCBR to help us in ensuring a productive, safe and positive environment for all.

By registering and attending the meeting, I confirm that I have read the Code of Conduct for the WCBR, and agree that it is my responsibility to be familiar with, and to abide by, its terms. I also attest that I will cooperate with any formal or informal inquiry into my behavior and/or actions at the Annual Meeting. I agree to be bound by the decisions of the Executive Subcommittee on Meeting Conduct, which may
take any action that it deems appropriate, including but not limited to exclusion from a current Annual Meeting (without refund) or from future meetings.

PHOTOGRAPHY & VIDEOGRAPHY POLICY

WCBR does not allow photography or videography of oral presentations, slides and/or posters without permission from the presenter. At the beginning of the presentation, the presenter must either grant permission to the audience and/or include an icon on the first slide or poster signifying photos or videos are allowed.

CONGRATS TO WCBR'S 2023 PIONEER AWARDEES!

Each year, WCBR solicits nominations for the annual Pioneer Awards. This tradition serves to recognize and honor pioneering scientists who demonstrate excellence in the field of neuroscience and have made invaluable contributions to WCBR over the years. Many worthy candidates were nominated this year and the WCBR Board of Directors and Executive Committee had the difficult task to select two candidates for recognition.

Marisela Morales, M.S., Ph.D.

2023 WCBR Pioneer Awardee

Dr. Marisela Morales is a Branch Chief of the Integrative Neuroscience Research Branch and Section Chief of Neuronal Networks Section in the Intramural Research Program (IRP) at the National Institute on Drug Abuse (NIDA) at the National Institutes of Health (NIH). She is also the NIDA IRP Associate Director of Technology.

She has been investigating the molecular and cellular composition of neuronal networks and how their different elements play a role in different aspect of neuronal transmission underlying animal behavior. She has discovered unanticipated neuronal phenotypes in the midbrain and forebrain, including neurons that co-release several neurotransmitters from the same axon or same axon terminal, and showed that these neurons play a role in reward, aversion, drug seeking behavior or pain. She is known particularly for her studies on neuronal diversity among ventral tegmental area neurons, their neuronal connectivity and role in motivated behavior. She was a co-leader of the NIDA Initiative to Promote Racial Equity, she is currently a member of the NIH Equity Committee and serves on the WCBR Board of Directors.

Phil Skolnick, Ph.D., D.Sc.

2023 WCBR Pioneer Awardee

Phil Skolnick is currently the Chief Scientific Officer at Opiant Pharmaceuticals. His career at the NIH intramural research program spanned 25 years, beginning with a postdoctoral fellowship in the laboratory of John W. Daly and ending as Senior Investigator and Chief, Laboratory of Neuroscience, NIDDK.

He left the NIH in 1997 to join Lilly Research Laboratories as a Lilly Research Fellow in Neuroscience and subsequently joined DOV Pharmaceutical, Inc. as its Chief Scientific Officer. In 2010, Skolnick returned to the NIH as the Director, Division of Therapeutics and Medical Consequences at NIDA prior to assuming his current position in 2017. Dr. Skolnick has co-authored more than 560 articles and edited six books spanning both basic and clinical neuropsychopharmacology. He was a founding editor of Current Protocols in Neuroscience and has served on the editorial advisory boards of more than a dozen journals. Skolnick is a Fellow of the American College of Neuropsychopharmacology (ACNP) and the American Society for Pharmacology & Experimental Therapeutics (ASPET). ASPET has recognized his body of work with the ASPET Award for Experimental Therapeutics and the Ray Fuller Lecture in the Neurosciences. He has also been recognized with the A.E. Bennett Award in Biological Psychiatry, an Anna-Monika Prize, the Donald F. Klein Lifetime Achievement Award from the American Society of Clinical Psychopharmacology, and multiple distinguished lectureships. Dr. Skolnick has been awarded the Doctor of Science, honoris causa by Long Island University (1993) and the University of Wisconsin-Milwaukee (1995).

Friday, January 20, 2023

6:00 PM - 6:30 PM
Welcome Reception for Newcomers, Travel Fellows and Mentors
Ballroom 1

6:30 PM - 7:30 PM
Welcome Reception
Ballrooms 2 & 3

Saturday, January 21, 2023

7:00 AM - 8:00 AM
Plenary Breakfast
Ballroom 1, 2 & 3

8:00 AM - 9:30 AM
Conference Welcome and Plenary Address
Ballroom 1, 2 & 3

Keynote: Race and the Brain: Insights From the Neural Systems of Emotion and Decisions
Elizabeth Phelps

9:45 AM - 11:15 AM
Pioneer Session #1:
Dr. Phil Skolnick, Ph.D., D.Sc.*
Superior

Treatment of Overdose in the Synthetic Opioid Era*
Pioneer: Phil Skolnick
Chair: Amy Newman

11:15 AM - 11:45 AM
Panel Chair Training Session
Cirque
David Devilbiss

**Not eligible for CME credit.*

Saturday, January 21, 2023

2:00 PM - 3:30 PM

Professional Development Session #1:
Magpie B

Designing Science Presentations: Simple Design Strategies to Improve Science Posters and Papers
Matt Carter

3:30 PM - 4:30 PM

Poster Session 1
Ballrooms 2 & 3

4:30 PM - 6:30 PM

Panel - Ballroom 1
Sex Differences in Brain Injury: Does it Matter?
Cole Vonder Haar (Chair), Kristen Pechacek, Olga Kokiko-Cochran, Rachel Rowe, Akiva Cohen (Co-Chair)

Panel - Magpie A
Mechanisms of Social Cognition: Insights From Neuroimaging, Computational Approaches and Psychopathology
Christina Carlisi (Chair), Dorit Kliemann, Caroline Charpentier, Tessa Rusch

4:30 PM - 6:30 PM

Panel - Magpie B
What Immediate Early Genes Can Tell Us About Memory and Brain Plasticity
Jason Shepherd (Chair),Christine Ann Denny (Co-Chair), Ivo Spiegel, Anne West, Yingxi Lin

Panel - Primrose A
Prefrontal Cortical Regulation of Aversive Emotional Processing
Laura DeNardo, Fabricio Do Monte, Roger Clem (Co-Chair), Joshua Johansen (Chair)

Panel - Primrose B
Feel Good Fuel: Mitochondrial Function in Reward Circuits
Fiona Hollis, Cali Calarco (Chair), Emily Witt, Sergio Dominguez-Lopez

Panel - Superior
Novel Insights Into the Brain Circuit Adaptations Underlying Substance Use Disorders
Adelaide Minerva, Abigail Polter, Stephan Lammel (Chair), Sung Han

Saturday, January 21, 2023

4:30 PM - 6:30 PM

Panel - Wasatch A
Neuroscience Education: The Power of Training Faculty to Incorporate Research Into Their Teaching
Sonsoles de Lacalle (Chair), Paul Ulrich, Christy Visaggi, Sonsoles de Lacalle, Thomas Clobes

Panel - Wasatch B
mTOR Signaling in Autism Spectrum Disorders
Stephen Smith (Chair), Smita Yadav, Helen Bateup, Damon Page

6:30 PM - 7:00 PM

Evening Refreshment Break
Ballrooms Lobby and Superior Lobby

7:00 PM - 8:30 PM

Panel - Ballroom 1
Sex Differences in Brain Injury: Does it Matter?
Cole Vonder Haar (Chair), Kristen Pechacek, Olga Kokiko-Cochran, Rachel Rowe, Akiva Cohen (Co-Chair)

Short Course - Ballroom 1
Using Microcontrollers for Neuroscience Research
Lex Kravitz (Chair), Jibran Khokhar, Jude Frie

7:00 PM - 8:30 PM

Panel - Magpie B
Lost in Vagus: Deregulation in Vagal Signaling in Health and Disease
Guillaume de Lartigue, Teresa Pitts, Jasenka Zubcevic (Chair)

Panel - Magpie B
Prodromal Synucleinopathy Neuroimaging Update
Kejal Kantarci, Daniel Huddleston (Chair), Xiaoping Hu

Short Course - Primrose A
Pipette-Free Drug for Repurposing CNS Disorders
Robert McCullumsmith (Chair), Sinead O'Donovan, Rammohan Shukla

Panel - Primrose B
Interactions Between Substance Use and Aging in Animal Models
Cassandra Gipson (Co-Chair), Mathieu Wimmer, Shameena Bake, Barry Setlow (Chair)

Saturday, January 21, 2023

7:00 PM - 8:30 PM

Panel - Superior

Mechanisms Linking Chronic Pain and Substance Use Disorders: A Focus on Pain Catastrophizing

Patrick Finan (Chair), Robert Edwards, Lara Ray, Vitaly Napadow

Panel - Wasatch A

Reefer Madness: Revisiting the Intersectionality Between Cannabis, the Endocannabinoid System, and Psychosis

Mary Torregrossa (Chair), Shinnyi Chou, Sierra Stringfield, Bryan Jenkins

7:00 PM - 8:30 PM

Panel - Wasatch B

Post-Traumatic Epilepsy Models and Biomarkers

Denes Agoston, John Wolf, Dominique Duncan (Chair)

Sunday, January 22, 2023

6:30 AM - 8:30 AM

Breakfast at Leisure

6:30 AM - 8:30 AM

Board of Director's Meeting

White Pine

7:30 AM - 9:30 AM

Panel - Ballroom 1

Incubation of Drug Craving: From Genes to Circuits to Humans

Yavin Shaham (Chair), Marina Wolf, Mathieu Wimmer, Ida Fredriksson, Muhammad Parvaz

Sunday, January 22, 2023

7:30 AM - 9:30 AM

Panel - Magpie A

Memory Engrams are Altered During Stress, Aging, and Anxiety

Kevin Sattler, Kirstie Cummings, Holly Hunsberger (Chair), Stephanie Grella

Panel - Magpie B

Brain Dynamics and Nonlinearity during Functional Reorganization

Stefan Posse (Chair), Todd Constable, Xiaoping Hu, Essa Yacoub

Panel - Primrose A

The Insula: An Integral Hub for Motivation and Affect

Amy Lasek, Samuel Centanni (Chair), Ashmita Mukherjee, Dennis Sparta

Panel - Primrose B

Synaptic Adhesion Molecules and Disease: From Molecules to Circuits

Katherine Roche (Chair), Tabrez Siddiqui, Adema Ribic, Marc Fuccillo (Co-Chair)

7:30 AM - 9:30 AM

Panel- Superior

I 'Snow' How You Feel: Using Rodent Models to Understand the Neurobiology of Empathy

James Burkett (Co-Chair), Weizhe Hong, Hee-Sup Shin, Monique Smith (Chair)

Panel - Wasatch A

Mapping Theoretical and Basic Research Findings of Cognitive Aging to Older Adult's Everyday Life Concerns

Natalie Ebner, Abbi Hernandez, Rachael Seidler (Chair), Joaquin Anguera

Panel - Wasatch B

Novel Tools to Map Adaptive and Maladaptive Effects of Reactive Astrogliosis in CNS Diseases

Milos Pekny (Chair), Jan Mulder, Rudolf Merkel

9:30 AM - 10:30 AM

Diversity and Inclusion Power Hour

Superior

Sunday, January 22, 2023

11:00 AM - 2:30 PM

Off-Site Excursion: Temple Square
Departs from Cliff Lodge Porte Cochere at 11:00 AM
Advance Sign-ups Required

3:00 PM - 3:30 PM

Data Blitz
Ballroom 1

3:30 PM - 4:30 PM

Poster Session II
Ballrooms 2 & 3

4:30 PM - 6:30 PM

Panel - Ballroom 1
Ketamine Can Get You High but is it a Better Lift?
Elyssa Margolis (Chair), Lakshmi Devi, Tommaso Di Ianni, Marjorie Levinstein, Matthew O'Meara

Panel - Magpie A
Function and Mechanism of Signaling Mediated by the Ionotropic Glutamate Receptors
Terunaga Nakagawa (Chair), Maria Kurnikova, Jakob von Engelhardt, Lonnie Wollmuth

4:30 PM - 6:30 PM

Panel - Magpie B
NADIA: Cholinergic Regulation of Neuronal Plasticity and Disruptions by Adolescent Alcohol
Fulton Crews (Chair), Ryan Vetreno, Lisa Savage, Kati Healey, Victoria Macht

Panel - Primrose A
Neural Mechanism Underlying Affective and Cognitive Interaction
Yi Zuo (Chair), Paul Marvar, Shaorong Ma, Kuan Hong Wang, David Leopold

Panel - Primrose B
Bottoms Up: The Gut-Brain Axis in Substance Use Disorders
Rebecca Hofford, Santiago Cuesta (Chair), Kevin Braunscheidel (Co-Chair), Michelle Ren

Panel - Superior
The Role of the Paraventricular Nucleus of the Thalamus in Motivated Behaviors
Jacqueline McGinty (Co-Chair), James Otis, Mario Penzo, Hao Li (Chair)

Sunday, January 22, 2023

4:30 PM - 6:30 PM

Panel - Wasatch A

Contributions of Locus Coeruleus Dysfunction to Neurodegenerative Disorders

Alexa Iannitelli (Co-Chair), Qi Yuan, Michael Kelberman (Chair), Neus Falgàs, Claire O'Callaghan

Panel - Wasatch B

Transformative Gene Therapy Strategies for Disorders of the Brain and Spinal Cord

Isabelle Aubert (Chair), Cassandra Dennys-Rivers, Rikke Hahn Kofoed, Kathrin Meyer

7:00 PM - 8:30 PM

Brain Talk Town Hall Panel

Ballroom 1

JEDI Guardians: Using Neuroscience Knowledge to Promote and Protect Justice, Equity, Diversity, and Inclusion in Schools, Companies, and Communities

Kyle Frantz (Chair), Elizabeth Phelps, Laura O'Dell, Stefano Cataldi

9:00 PM - 11:00 PM

Karaoke

SeventyOne Lounge

Monday, January 23, 2023

6:30 AM - 8:30 AM

Breakfast at Leisure

6:30 AM - 8:00 AM

Travel Fellow and Mentor Breakfast

Maybird

7:30 AM - 9:30 AM

Panel - Ballroom 1

Basal Ganglia Circuit Dysfunction in Parkinson's Disease

Nicolas Tritsch, Chris Ford (Chair), Alexandra Nelson, Thomas Hnasko

Monday, January 23, 2023

7:30 AM - 9:30 AM

Panel - Magpie A

Auditory System: From Cell Diversity to Behavior

Alfonso Junior Apicella (Chair), Li Zhang (Co-Chair), Patrick Kanold, Robert Liu, Ramnarayan Ramachandran

Panel - Magpie B

Consciousness and Unconsciousness in People and Animals

Kathleen Vincent, Anthony Hudetz, Ken Solt (Chair)

Panel - Primrose A

Exploring the Neurophysiological Effects of Potentially Therapeutic Psychedelic Compounds

Alfred Kaye, Gavin Schmitz (Chair), William Wetsel, Melissa Herman (Co-Chair)

Panel - Primrose B

Neural Circuit Mechanisms Underlying the Motivational Control of Behavior

Estefania Azevedo, Robert Froemke, Dhananjay Bambah-Mukku, Sarah Stern (Chair)

7:30 AM - 9:30 AM

Panel - Superior

Getting Motivated During Stressful Times Throughout the Lifespan

Debra Bangasser (Chair), Jared Young (Co-Chair), Amelia Cuarenta, Deena Walker, Zoe McElligott

Panel - Wasatch A

The Effects of Social Interaction and Exercise on SUD-Related Behaviors and Associated Neurobiology

Jennifer Wenzel (Chair), Mark Smith, Jonathan Chow, Margaret Rice, Natalie Zlebnik (Co-Chair)

Panel - Wasatch B

From Bunny Slope to Black Diamond: Expert Perspectives on Community Outreach to Enhance Stem Education

Michael Stefanik, (Chair), Patrice Darby (Co-Chair), Christopher Evans, Karagh Brummond, Dominique Duncan, Amanda Roberts

Monday, January 23, 2023

9:45 AM - 11:15 AM

Pioneer Session #2:
Dr. Marisela Morales, M.S., Ph.D.
Superior

Ventral Tegmental Area Neuronal Diversity, Connectivity, Unanticipated Types of Neurotransmission and Behavior
Pioneer: Marisela Morales
Chair: Elyssa Margolis
Investigators: David Barker, David Root

11:30 AM - 2:00 PM

Off-Site Excursion:
Clark Planetarium
Departs from Cliff Lodge Porte Cochere at 11:30 AM
Advance Sign-ups Required

2:00 PM - 3:30 PM

Professional Development Session #2
Magpie B

Mid-Career Transitions
Erik Carlson, Lloyd Fricker, David Devilbiss, John Neumaier, Kyle Frantz

3:30 PM - 4:30 PM

Poster Session III
Ballrooms 2 & 3

4:30 PM - 6:30 PM

Panel - Ballroom 1
Molecule Monitoring in the Study of Substance Use Disorders
Snigdha Mukerjee (Co-Chair), Leslie Sombers, Suzanne Nolan (Chair), Jordan Yorgason, David Lovinger

Panel - Magpie A
Perception to Action: Processing Sensory Signals in Complex Environments
Sandra Kuhlman (Chair), Renata Batista-Brito, Michael Goard, Huizhong Tao

Panel - Magpie B
Cell-Type Specific and Activity Dependent Transcription Regulation in Cocaine-Activated Ensembles
Katherine Savell, Kimberly Thibeault, Marine Salery (Chair), Philipp Mews (Co-Chair)

Panel - Primrose A
Stress and Trauma Effects on Motivated Behavior
Nick Hollon (Chair), Lauren Burgeno, Matthew Wanat, Abigail Schindler, Christopher Olsen

Monday, January 23, 2023

4:30 PM - 6:30 PM

Panel - Primrose A
Stress and Trauma Effects on Motivated Behavior
Nick Hollon (Chair), Lauren Burgeno, Matthew Wanat, Abigail Schindler, Christopher Olsen

Panel - Primrose B
Neuronal Heterogeneity of the Dorsal Raphe and its Role in Motivated Behaviors
Marisela Morales (Chair), John Neumaier, David Prober, Flavia Barbano (Co-Chair), Mitchell Spring

Panel - Superior
Pain Neurocircuits: Nociception, Affect and Opioid Seeking
Yarimar Carrasquillo, Jessica Wojick, Nicolas Massaly (Chair), Jose Moron-Concepcion

Panel - Wasatch A
Postsynaptic Signaling at Glutamatergic Synapses
Johannes Hell (Chair), Andres Maricq, Weifeng Xu, Mark Dell'Acqua

4:30 PM - 6:30 PM

Panel - Wasatch B
New Kid on the Appetite Block: Regulation of Ingestive Behaviors by the Parasubthalamic Nucleus
Marie Barbier, Matt Carter (Co-Chair), Candice Contet (Chair), Jiahao Ye

6:30 PM - 7:00 PM

Evening Refreshment Break
Ballroom Lobby and Superior Lobby

7:00 PM - 8:30 PM

Short Course - Ballroom 1
Novel Paradigms and Automated Behavioral Analyses for the Study of Motivation and Addiction
Yujia Hu, Christie Fowler, Jibran Khokhar

Short Course - Magpie A
A Helicopter-View of the Chutes, Glades, Bowls and Peaks of Clinical Brain Stimulation
Joshua Brown (Chair), Tracy Barbour, Darin Dougherty, Nick Trapp

Monday, January 23, 2023

7:00 PM - 8:30 PM

Panel - Magpie B

Visualizing RNA Dynamics in Living Animals

Sulagna Das, Andrej Luptak, Oswald Steward (Chair)

Panel - Primrose A

Brain Positron Emission Tomography in Substance Use Disorders: Studies With Pharmacological Challenges

Peter Manza, Ansel Hillmer, Corinde Wiers (Chair)

Panel - Primrose B

Diverse Model Systems to Interrogate Psychiatric Disorders: Challenges and Opportunities*

Elizabeth Tunbridge (Chair), Wilfried Haerty, Brady Maher, Thomas Hyde

7:00 PM - 8:30 PM

Panel - Superior

Defensive Survival Mechanisms in Neuroethological Models of Fear

Annie Ly (Chair), Romain Durand-de Cuttoli, Courtney Wilkinson, Dean Mobbs

Panel - Wasatch A

Emerging Issues of Motor Thalamus

Jun Ding (Chair), Tianyi Mao, John Huguenard (Co-Chair)

Panel - Wasatch B

Alpha -Synuclein Function in Health and Disease

Sreeganga Chandra, Jacqueline Burré, Hong-yuan Chu (Chair)

*Not eligible for CME credit.

Tuesday, January 24, 2023

6:30 AM - 8:30 AM

Breakfast at Leisure

7:30 AM - 9:30 AM

Panel- Ballroom 1

Immune Signaling Mechanisms of Pathology in Addiction

Fulton Crews (Chair), A. Leslie Morrow (Co-Chair), Leon Coleman, Carolina Haass-Koffler, M. Foster Olive, Rajesh Miranda

Panel - Magpie A

Parallel Tracks: Developing New Disease Models and New Therapies for the Treatment of Parkinson's Disease*

Janelle Drouin-Ouellet, Alvin Joselin, Anurag Tandon (Chair), Warren Hirst

Panel - Magpie B

Understanding Abnormal Excitability in Autism Spectrum Disorders: Insights From New Models and Approaches

Michelle Antoine, Anis Contractor, Anubhuti Goel, Vitaly Klyachko (Chair)

7:30 AM - 9:30 AM

Panel - Primrose A

Calorie Dense Energy Sources Reshape the Brain's Motivation Circuits

Richard O'Connor (Chair), Estefania Azevedo, Dan Christoffel (Co-Chair), Stacey Gorniak

Panel - Primrose B

Neurobiology of Binge Eating and Food 'Addiction': A Translational Perspective

Marc Potenza, Morgan James (Chair), Jessica Barson (Co-Chair), Samantha Fortin

Panel - Superior

The In-and Outs of Monoamine Transporters – Traversing Conformational Bias Toward Novel Therapeutics

Amy Newman, Freja Herborg (Chair), Ali Salahpour, Ulrik Gether

Panel - Wasatch A

Enabling Axon Regeneration in the Adult Nervous System

Alexandra Byrne (Co-Chair), Valeria Cavalli, Alyson Fournier, Cedric Geoffroy (Chair)

**Not eligible for CME credit.*

Tuesday, January 24, 2023

7:30 AM - 9:30 AM

Panel - Wasatch B

Exploration of Novel Mechanisms of Psychiatric Illness Reveals Metabolic Changes Across Translational Substrates

Robert McCullumsmith (Chair), Consuelo Walss-Bass, Margaret Hahn, Sinead O'Donovan, Amy Ramsey

10:00 AM - 11:30 AM

Smitty Stevens Ski Race

Race Hill - Lower Wilbere Ridge

11:30 AM - 1:30 PM

Mountain Lunch

Golden Cliff/Eagles Nest

3:30 PM - 4:30 PM

Poster Session V

Ballrooms 2 & 3

4:30 PM - 6:30 PM

Panel - Ballroom

Striatal and Non-Striatal Dopamine Signaling in Motivated Behaviors, Learning, and Affective States

Allyson Friedman, Erin Calipari, Arthur Godino, Carole Morel (Chair)

4:30 PM - 6:30 PM

Panel - Magpie A

Serotonin in Learning and Reward

Catia Teixeira, Marisela Morales, Mitchell Spring (Co-Chair), Katherine Nautiyal (Chair)

Panel - Magpie B

Recent Advances in Epileptology: Seizure Detection, Neuroimaging and Status Epilepticus

Claude Wasterlain, Sándor Beniczky, Lars H. Pinborg, Olaf Paulson (Chair)

Panel - Primrose A

Neurobiology of Circadian Rhythm and Sleep Alterations in Substance Use Disorders

Rui Zhang, Mackenzie Gamble, Utsav Gyawali (Chair), Andrew Kesner

Panel - Primrose B

How the Gut Talks to the Brain to Influence Motivation and Reward

Sam Bacharach (Chair), Laura Rupprecht, Nicholas DiPatrizio, Guillaume de Lartigue, Mark Rossi

Tuesday, January 24, 2023

4:30 PM - 6:30 PM

Panel - Superior

Translational Insights Into Opioid Use Disorder From Different Rodent Models of Opioid Use

Lori Knackstedt (Chair), Devin Mueller, David Martin, Jesse Schank, Marek Schwendt

Panel - Wasatch A

Slaloming Through Nanocolumns

Carolyn Brown, Daniel Choquet, Katharine Smith (Chair), Kristen Harris

4:30 PM - 6:30 PM

Panel

Wasatch B

The Astrocyte-Neuron Interaction in Reward Circuitry: Endocannabinoid, Plasticity and Motivation

Miguel Lujan (Co-Chair), Jose Noriega, Janay Franklin, Eden Harder, Lanyuan Zhang (Chair)

6:30 PM - 7:30 PM

WCBR Business Meeting

Ballroom 1

7:30 PM - 9:30 PM

Special Poster Session and Reception

Ballrooms 2 & 3

Wednesday, January 25, 2023

6:30 AM - 8:30 AM

Breakfast at Leisure

6:30 AM - 8:30 AM

Board of Directors Meeting

White Pine

7:30 AM - 9:30 AM

Panel - Ballroom 1

From Cells to Circuits: New Frontiers in Motivation and Reward

Melissa Sharpe (Chair), Erin Calipari (Co-Chair), James Otis, Moriel Zelikowsky

Wednesday, January 25, 2023

7:30 AM - 9:30 AM

Panel - Magpie A

Excitatory Synapse Ski for Complexity: Mechanisms of Disease and Plasticity

Martin Hruska, Elva Diaz (Chair), Yael Stern-Bach, Matthew Dalva (Co-Chair)

Panel - Magpie B

Promising Targets for Slowing Brain Aging

Natalie Ebner (Chair), Jennifer Bizon, Perla Moreno-Castilla, Mara Mather, Teal Eich

Panel - Primrose A

Critical Developmental Periods for Vulnerability to Substance Use and Psychopathology

Alexandra Potter (Chair), Catharine Winstanley, Erik Garcia, Scott Mackey

Panel - Primrose B

NMDA Receptor Signaling in Synaptic Function and Plasticity

Françoise Coussen-Choquet, Karen Zito, Pablo Castillo, Ulli Bayer (Chair)

7:30 AM - 9:30 AM

Panel - Superior

The Fault in Our Stars: Astrocytes as Key Players in Addictive and Depressive Behaviors

Anna Kruyer (Chair), Ciaran Murphy-Royal (Co-Chair), Jacqueline-Marie Ferland, Eric Parise

Panel - Wasatch A

Multi-Omics Analysis of Neural Plasticity During Memory Consolidation and Sleep

Iva Zovkic, Stefano Brigidi, Sara Aton, Graham Diering (Chair)

Panel - Wasatch B

Ovarian Hormone Regulation of Motivation and Emotion: Implications for Psychiatric Disease

Lillian Brady, Laura Been, Elizabeth Lucas (Chair), Mohammed Milad

Wednesday, January 25, 2023

11:00 AM - 3:00 PM

Off-Site Excursion:
The Leonardo &
Downtown Salt Lake City
Departs from Cliff Lodge
Porte Cochere at 11:00 AM
Advance Sign-ups Required

4:30 PM - 6:30 PM

Panel - Ballroom 1
Defining and Manipulating Neural Circuits That Govern Reward-Related Behaviors
Michael Scofield (Co-Chair), Alexa Zimbelman, Kathleen Bryant, Michael Stefanik (Chair)

Panel - Magpie A
Diet, Exercise, and Gut Metabolism: Convergent Molecular Pathways Affecting Brain Function and Behavior
Drew Kiraly, Marcelo Wood (Co-Chair), Philipp Mews (Chair), Steven Fordahl

Panel- Magpie B
Novel Functions for proSAAS in the Regulation of Feeding, Body Weight, Drug Abuse, and Neurodegenerative Disease
Lloyd Fricker (Co-Chair), Daniel Morgan (Chair), Amanda Fakira, Erin Bobeck, Iris Lindberg

4:30 PM - 6:30 PM

Panel - Primrose A
Pleasure Despite Pain: Interventions and Mechanisms That Promote Resilient Adaptation to Chronic Pain
Patrick Finan (Chair), Fadel Zeidan, Anne Baker

Panel - Primrose B
Stress Adaptation Versus Maladaptation: Implications for Diseases Susceptibility and Resilience
Debra Bangasser, Jason Radley, Erica Glasper (Chair), Mathias Schmidt

Panel - Superior
Serotonergic Roles in Addiction and Motivation
Thomas Jhou (Chair), Christina Merritt, Catharine Winstanley

Panel - Wasatch A
Chronic Opioid Induced Neuroadaptations: Focus on Hyperalgesia and Individual Differences
Elyssa Margolis, David Barker, Renata Marchette (Chair)

Wednesday, January 25, 2023

4:30 PM - 6:30 PM

Panel - Wasatch B

Naturalistic Neuroimaging and Psychiatry: Where Do We Go From Here?*

Oliver Robinson (Chair), Emily Finn, Tamara Vanderwal, Peter Kirk, Gaurav Patel

6:30 PM - 7:30 PM

Cocktail Hour

Ballroom Lobby

7:30 PM - 11:00 PM

Awards Banquet and Dance

Ballroom 1, 2 & 3

*Not eligible for CME credit.

POSTER SESSION I
Saturday, January 21, 2023
3:30 PM - 4:30 PM

SA1. Interactive Digital Media to Reduce Medical Student Depression and Alcohol Use
Bradley Tanner

SA2. Sex-Dependent Features of Oxycodone Self-Administration and Their Ranked Association With Reinstatement of Drug-Seeking in Rats
Gillian Driscoll

SA3. Examination of the Role of VTA→IC DA Signaling on *Ethanol-Directed Behaviors*
Kajol Sontate

SA4. Social Interaction Shapes Cocaine Reward and Aversion in Male and Female Rats
Jennifer Wenzel

SA5. The Role of the Gut-Brain Axis in Intravenous Fentanyl Self-Administration
Michelle Ren

SA6. Chronic Intermittent Ethanol Drinking Alters Brain Endocannabinoid System and Cannabinoid Receptor Neutral Antagonism Decreases Drinking
Russell Dulman

SA7. Sex Differences in the Impact of Electronic Nicotine Vapor on Corticotropin-Releasing Factor Receptor 1 Neurons in the Mouse Ventral Tegmental Area
ManHua Zhu

SA8. Genetic Variation Influences on Learning, Memory and Alcohol Metabolism
Prescilla Garcia-Trevizo

SA9. Chronic Alcohol Exposure Disrupts Orbitofrontal-Premotor Circuit Transmission of Action-Related Information
Christina Gremel

POSTER SESSION I
Saturday, January 21, 2023
3:30 PM - 4:30 PM

SA10. Changes in Striatal Dopamine Release, Sleep, and Behavior During Spontaneous Δ-9-Tetrahydrocannabinol Abstinence in Male and Female Mice
Andrew Kesner

SA11. Morphine's Opposing Actions Define Opioid Preference Versus Seeking
Sung Han

SA12. Individual Differences in Susceptibility to Postpartum Mood Changes and Underlying Neuroimmune and Resting State Neural Connectivity in Sprague Dawley Rats
Janace Gifford

SA13. The Expression of Key Hub Genes Within the Nucleus Accumbens Mediates Resilience to Chronic Stress
Trevonn Gyles

SA14. A Characterization of Social Defeat Stress and its Impacts on Depressive-Like Behavior in Rats
Sara Pickernell

SA15. Characterization of Endogenous Opioid Systems Within the Paraventricular Nucleus of the Thalamus
Sofia Shirley

SA16. Sex-Specific Effects of Psychedelic Drug Exposure on Central Amygdala Reactivity and Behavioral Responding
Devin Effinger

SA17. Studying the Impact of Shank3-Deficiency on the Mesoaccumbens Pathway of Reward
Marie Barbier

SA18. Modulation of Potassium Channels Preserves Temporal Fidelity in Sensory Processing
Leonard Kaczmarek

SA19. Distinct Dopamine Signaling in Action Sequence Learning Driven by Reward Predictive Stimulus
Robin Magnard

SA20. Ventral Tegmental Area Release of Glutamate or GABA From Local Neurons Play Distinct Roles in Aversion, Reward and Feeding Behavior
Huiling Wang

POSTER SESSION I
Saturday, January 21, 2023
3:30 PM - 4:30 PM

SA21. Sleep Deprivation Decreases Dendritic Spines and Expression of CaMKIIα and SST in Hippocampal Neurons Following Contextual Fear Learning
Barbara Gisabella

SA22. Delineation of the G Protein-Coupled Receptor Kinase Phosphorylation Sites Within the D1 Dopamine Receptor and How They Regulate Receptor Function
David Sibley

SA23. Single Channel Characteristics of Conductance and Non-Conductance Modifying Allosteric Modulators of the NMDA Receptor at the Channel Gate
Elijah Ullman

SA24. RNA Binding Proteins are Enriched in Tau Interactions and Dysregulated Across Tauopathy
Tomas Kavanagh

SA25. High Levels of Cell-Free Mitochondrial DNA Deletions in Cerebrospinal Fluid From Patients With Idiopathic, But Not LRRK2, Parkinson's Disease
Ramon Trullas

SA26. Quantification of Intrathecal Gadolinium Pharmacokinetics and Adeno Associated Virus Serotype 9 (AAV9) Biodistribution via Lumbar Puncture Versus Automated Catheter Infusion System
Gabryel Conley Natividad

SA27. 3D Computational Fluid Dynamics and In Vitro Modeling of Intrathecal Cerebrospinal Fluid Pharmacokinetics Predicts In Vivo Solute Transport of Gadolinium and AAV9 Co-infusion in Non-Human Primates
Bryn Martin

POSTER SESSION I
Saturday, January 21, 2023
3:30 PM - 4:30 PM

SA28. Anesthetic Effects and Impact of Oxytocin on Electrically Evoked Fast-Scan Cyclic Voltammetry Dopamine Signals in Dorsal Striatum of the Rat Brain
David Daberkow

SA29. Traumatic Brain Injury Reduces Conditioned Reinforcement and Optimal Decision-Making on a Cued Rodent Gambling Task
Sarah Wampler

SA30. Analysis of Endogenous and Transplanted Stem Cell Populations Following Traumatic Brain Injury in Adult Zebrafish
Jeffery Plunkett

SA31. Poor Glycemic Control is Associated With Worse Blood-Brain Barrier Disruption in Ischemic Stroke Patients
Richard Leigh

SA32. Novel, Thalidomide-Like, Non-Cereblon Binding Drug Tetrafluorobornylphthalimide Mitigates Inflammation and Brain Injury
Nigel Greig

SA33. Leveraging Mouse and Rat Brain Atlases to Standardize Brain-Wide Mapping in Serial Sections and Cleared Intact Brain Volumes Across Experiments
Shane Baldwin

SA34. Chronic Administration of JWH-133 (Cannabinoid Receptor 2 Agonist) Increases Ectopic Ovarian Tumor Growth and Endocannabinoids Levels in Immunocompromised SCID Female Mice
Melissa McHann

SA35. A Dopaminergic System Promoting Sniffing
Natalie Johnson

SA36. Chronic Morphine Has Opposing Effects on Opioid Signaling Within a Thalamo-Cortico-Striatal Microcircuit
Elizabeth Jaeckel

POSTER SESSION I
Saturday, January 21, 2023
3:30 PM - 4:30 PM

SA37. The Influence of Mood State on Self-Assessment in Patients With Schizophrenia and Bipolar Disorder
Felicia Gould

SA38. Bacteroides Spp. HB-32 Rescues Behavioral Phenotypes in Sleep Deprivation- and Social Defeat Stress-Induced Models of Depression
Stephen Skolnick

DATA BLITZ
Sunday, January 22, 2023
3:00 PM - 3:30 PM

1. Chemesthetic Perception Gates Orosensory Acceptance of Alcohol
Snigdha Mukerjee

2. Dissociable Control of Motivation and Goal-Directed Behavior by Distinct Ventral Striatal Dopamine Receptors
Juan Enriquez-Traba

3. Can Porn Be Addictive? Results of Comparative VBM, DTI and fMRI Studies and Randomized Clinical Trial
Mateusz Gola

4. Amygdalar-Cortical Circuit Determinants of Social Isolation-Associated Alcohol Consumption
Reesha Patel

5. Emerging Activity Dynamics and Noradrenergic Modulation of Prelimbic Cortical Neuronal Ensembles During Heroin Seeking
Elizabeth Doncheck

6. Highly Localized Dopamine Signals Evoke Post-Synaptic Responses in Striatal Medium Spiny Neurons
Andrew Yee

POSTER SESSION II
Sunday, January 22, 2023
3:30 PM - 4:30 PM

SU1. The Role of the Lateral Habenula in Individual Susceptibility to Opioid Abuse
Christopher O'Brien

SU2. Inhalation Self-Administration of Heroin and Nicotine in Middle Aged Rats
Michael Taffe

SU3. The Impact of EcoHIV Infection on Cocaine-Related Behaviors
Qiaowei Xie

SU4. Measuring the Effect of Neuropathic Pain on Drug-Seeking Ensembles in the DMPFC
Bailey Sarka

SU5. The Ventral Tegmental Area has Glutamatergic Neurons That Play a Role in Cocaine Seeking-Behavior
Flavia Barbano

SU6. Chemesthetic Perception Gates Orosensory Acceptance of Alcohol
Snigdha Mukerjee

SU7. Enhanced Excitability and Excitatory Transmission in Noradrenergic NTS Neurons Following Precipitated Morphine Withdrawal
Anthony Downs

SU8. Can Porn Be Addictive? Results of Comparative VBM, DTI and fMRI Studies and Randomized Clinical Trial
Mateusz Gola

SU9. Compartment-Specific Mesolimbic Dopamine Dynamics in Contingency Learning
Suzanne Nolan

SU10. Predicting Relapse With the Entire Animal's History of Cocaine-Evoked Dopamine Responses
Miguel Lujan

POSTER SESSION II
Sunday, January 22, 2023
3:30 PM - 4:30 PM

SU11. Crispr-Based Manipulation of Kv7 (KCNQ) Channel Subunits Reveals Unique Contributions to Striatal Neuron Activity
Emily Jorgensen

SU12. Emerging Activity Dynamics and Noradrenergic Modulation of Prelimbic Cortical Neuronal Ensembles During Heroin Seeking
Elizabeth Doncheck

SU13. Amygdalar-Cortical Circuit Determinants of Social Isolation-Associated Alcohol Consumption
Reesha Patel

SU14. OPEN BOARD

SU15. Lesion Symptom Mapping of Appetite
Nick Trapp

SU16. Dissociable Control of Motivation and Goal-Directed Behavior by Distinct Ventral Striatal Dopamine Receptors
Juan Enriquez-Traba

SU17. Novel Mitochondrial Mechanisms Assessed in Stem Cell-Derived Neurons to Treat Bipolar Disorder and Reduce Suicide
Elizabeth Jonas

SU18. Combined Anti-Psychotic Treatment in Acute Manic Psychosis
Bradley Tanner

SU19. Identification of Dysregulated Micro-RNAs in Human Brain Tissue From Psychiatric Patients
Erik Kaadt

SU20. MRI Quantification of Ophthalmic and Brain Structural and Physiologic Changes Due to Long-Duration Spaceflight
Katherine Warthen

SU21. Locally Sustained Interactive Oscillations in a Quantitative Neural Population Model
Yu Qin

POSTER SESSION II
Sunday, January 22, 2023
3:30 PM - 4:30 PM

SU22. Computational Modeling of the Processes Underlying Cognitively Effortful Decision Making in Rats
Claire Hales

SU23. The Gut Microbiome Modifies Risky Decision-Making after Traumatic Brain Injury, Potentially via Serotonin
Kris Martens

SU24. Distinct VTA Glutamatergic Populations Differentially Signal Reward Value and Economic Decision Making
Dillon McGovern

SU25. Decoding the Molecular Computation by CAMKII Holoenzymes That Directs Synaptic Plasticity
Carolyn Brown

SU26. Utilization of Remote Aerobic Exercise Monitoring to Facilitate Exercise Adherence in People With Parkinson's Disease
Anson Rosenfeldt

SU27. The Impact of Blood-Brain Barrier Modulation by Focused Ultrasound on Oligodendrogenesis
Kate Noseworthy

SU28. Lysosomal Lipid Accumulation in Neurons Promotes Early Alzheimer's Pathology by Preventing Lysosomal Clearance of Intraneuronal A**β**1-42
Alexandra Barnett

SU29. Modal Analysis of Natural Vibration Frequencies of the Brain and Head
Turner Jennings

SU30. Detailed Mapping of Stroke-Induced Molecular Changes in a Mouse Model Using Spatially Resolved Transcriptomics Approach
Tianyu Zheng

SU31. Development of Drug Resistance in Seizure Suppression With Long Term MTOR Inhibitor Treatment in a Mouse Model of TSC
Anne Anderson

POSTER SESSION II
Sunday, January 22, 2023
3:30 PM - 4:30 PM

SU32. Highly Localized Dopamine Signals Evoke Post-Synaptic Responses in Striatal Medium Spiny Neurons
Andrew Yee

SU33. Scanned Line Angular Projection Two Photon Laser Scanning (SLAP2) Microscopy for Real-Time (Kilohertz Rates) Volumetric in Vivo Imaging at Subcellular Resolution
Aidan E. Sullivan

SU34. Brainwide Tracing of Monosynaptic Inputs to Ventral Tegmental Area Glutamate-GABA Co-Transmitting Neurons
Emily Prevost

SU35. Research Opportunities from the Archived Neuroanatomic Slide Collections of the National Museum of Health and Medicine
Daniel Perl

SU36. Correlation Between Subcutaneous Adipose Tissue of the Head and Body Mass Index: Implications for Functional Neuroimaging
Stacey Gorniak

SU37. JNK Signaling Dose and Sex-Dependent Effects on CP55,940 Tolerance to CB1 Desensitization-Resistant Mutant Mice
Josee Guindon

POSTER SESSION III
Monday, January 23, 2023
3:30 PM - 4:30 PM

M1. D-Cysteine Ethyl Ester Disrupts Acquisition of Fentanyl Seeking While Preserving Fentanyl-Induced Motoric and Analgesic Efficacy
Devin Mueller

M2. Investigation of the Necessity and Specificity of the DMPFC Cocaine Seeking Ensemble
Shuai Liu

M3. Investigating the Neurobiological Mechanisms Underlying the Conditioned Reinforcing Effects of Cocaine
Lauren Rysztak

M4. Ethanol Potentiates Fentanyl-Induced Respiratory Depression
Emma Frye

M5. Sex-Dependent Effects of Alcohol and Oxycodone Polysubstance Use
Yueyi Chen

M6. Morphine Exposure and Withdrawal Alters Sleep Patterns in Male and Female Mice
Madigan Bedard

M7. Impact of Ketamine on Cue-Induced Reinstatement of Cocaine Self-Administration in Rats
Angela Gonzalez

M8. Maintenance of Synaptic Function at the Drosophila Neuromuscular Junction is Regulated by Alpha-Ketoglutarate Availability
Jill Farnsworth

M9. The Contributions of Neuronal Nitric Oxide Synthase (nNOS) to Cued-Cocaine Seeking
Adam Denton

M10. Mutant Mice Expressing an Internalization-Resistant Form of CB1R Display Altered Cannabinoid Response and Tolerance
Daniel Morgan

M11. OPEN BOARD

POSTER SESSION III
Monday, January 23, 2023
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M12. Social Isolation and Footshock Stress Produce Aggression that is Behaviorally and Biologically Distinct
Michael Conoscenti

M13. OPEN BOARD

M14. Old Brains – New Ideas: A Non-Coding RNA Perspective
Rolf Søkilde

M15. Differential Serum and Brain Levels of CACNA1C in Subjects With Bipolar Disorder
Harry Pantazopoulos

M16. Glucocorticoid Regulation of Striatal Dopamine Transmission
Ashley Holloway

M17. Leveraging Analogs of Cardiac HCN -Bradine Drugs to Regulate Dopamine Activity and Achieve Antidepressant Effects
Emily Teichman

M18. Cannabidiol (CBD) as a Treatment for Fragile X Syndrome (FXS) and Autism Spectrum Disorder (ASD)
Ilse Gantois

M19. Dopamine D2 Receptor Mutations and Hyperkinetic Movement Disorders
Kim Neve

M20. Role of D1- and D2-RECEPTOR Prefrontal-Accumbens Circuits in Cognitive Flexibility and Stress-Related Pathology
Matthew Hearing

M21. Stress-Resilient Mice Optimize Subjective Value and Food Security on an Economic Foraging Task
Romain Durand-de Cuttoli

M22. Stimulation of the Rostromedial Tegmental Nucleus Induces Long-Lasting Avoidance Behavior
Jacob Watson

M23. Melanocortin-4 Receptor Control of Striatal-Dependent Action Selection
Elizabeth Heaton

POSTER SESSION III
Monday, January 23, 2023
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M24. Calcium Activity is a Degraded Estimate of Spikes
Evan Hart

M25. Validation of a Digital Therapeutic to Improve Gait Performance in Parkinson's Disease: The Dual-Task Augmented Reality Treatment (DART) Platform
Anson Rosenfeldt

M26. Trem2R47H NSS; 5xFAD Mice Display Age/Disease Progression-Dependent Changes in Plaques and Plaque-Associated Microglia, and Increased Plasma Neurofilament Light Chain
Kim Green

M27. Oxytocin Can Help Prevent Opioid-Induced Respiratory Depression
David Mendelowitz

M28. Caveolae-Mediated Spontaneous Transient Vasospasm After Ischemic Stroke
Luis Tovar-y-Romo

M29. Locus Coeruleus-Noradrenergic System Impairment After Repeated Mild Traumatic Brain Injury
David Devilbiss

M30. The Lateral Preoptic Area Controls the Effects of Social Isolation on Mouse Courtship Behavior and Song
Erin Carroll

M31. Designer Molecules of the Synaptic Organizer MDGA1 Reveal 3D Conformational Control of Biological Function
Gabrielle Rudenko

M32. The Psychedelic 5-HT2A/2C Agonist DOI Influences Nucleus Accumbens Dopamine Signaling During Reward Prediction
David Martin

M33. G-Protein Coupled Receptor Activation Based (GRAB) Photometery Reveals Serotonin Release During Reward Consumption in the Dorsal Striatum
Mitchell Spring

POSTER SESSION III
Monday, January 23, 2023
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M34. Barriers to Entrepreneurship for Women Neuroscientists
Bradley Tanner

M35. Exposure to SNC-80 or Persistent Pain Alters Delta Opioid Receptor Signaling in Anterior Cingulate Cortex Parvalbumin Neurons
Marie Walicki

M36. Characterization of a Nociceptive Amygdala to Accumbens Neural Circuit
Jessica Wojick

M37. Combined Analysis of Caudate and DLPFC Transcriptomes Defines Two Molecular Subtypes of Schizophrenia
C. Harker Rhodes

POSTER SESSION IV
Tuesday, January 24, 2023
3:30 PM - 4:30 PM

T1. Adolescent Nicotine Exposure Facilitates Punishment-Resistant Opioid Self-Administration and Increases Perineuronal Net Density Within Insular Cortex in Adulthood
Sarah Honeycutt

T2. Chronic Ethanol Vapor Exposure in Adult Rats Reduces Behavior Flexibility
Yifeng Cheng

T3. Striatal Mors Have Divergent Effects on Cocaine and Opiate Behaviors
Bailey Remmers

T4. Chemogenetic Excitation of the Lateral OFC Increases Likelihood of Risky Drug Taking under Threat of Punishment
Zackari Murphy

T5. Extended Kappa-Opioid Receptor Antagonism Reduces Opioid Self-Administration in Dependent Mice
Lyndsay Hastings

T6. Individual Vulnerability to Predator Scent Stress Enhances Oxycodone-Seeking in Rats
Courtney Wilkinson

T7. Kappa Opioid Control of a GABAergic Stress-Sensitive Circuit Involved in Reinstatement
Valentina Martinez Damonte

T8. Measuring Activity in Corticostriatal Neuronal Ensembles From the Onset of Heroin Use to Relapse
Rachel Clarke

T9. Multiomic Profiling of the Rat Nucleus Accumbens Reveals Cell-Type Specific Chromatin Remodeling and Transcriptional Alterations After Cocaine Experience
Jennifer Tuscher

T10. Ex Vivo Optical Imaging of Calcium and Dopamine Dynamics in Primate Ventral Tegmentum Reveals Synaptic Plasticity Signatures of Chronic Ethanol-Induced Cognitive Dysregulation
Kirsty Erickson

POSTER SESSION IV
Tuesday, January 24, 2023
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T11. Neuronal Correlates of Hyperalgesia and Somatic Signs of Heroin Withdrawal in Male and Female Mice
Yocasta Alvarez-Bagnarol

T12. 3D Optogenetic Interrogation of Prelimbic Reward Learning Ensembles
Roger Grant

T13. Assessing the Effects of ΔFOSB Induction on the in Vivo Activity of Nucleus Accumbens Medium Spiny Neurons
Tamara Markovic

T14. Dopamine and Calcium-Indicated Activity in the Dorsal Striatum during the Transition to DLS Dopamine-Dependent Cocaine Seeking and Pavlovian Cue Extinction
Brooke Bender

T15. A Subset of Dorsal Raphe Glutamatergic Neurons Relays Rewarding Information to the Ventral Tegmental Area
Rodrigo Osnaya

T16. Characteristics of DMPFC Astrocyte Dynamics During Natural- and Drug-Reward Seeking Behaviors
Jacqueline Paniccia

T17. Effects of Sex and Age on Nicotine Vapour Reward, Withdrawal, Pharmacokinetics, and Brain Activity
Jude Frie

T18. Adolescent Nicotine Enhances Adult Morphine Reward by Altering Ventral Tegmental Area GABA Circuits
Ruthie Wittenberg

T19. The Role of GPR171 in Depression in Females
Megan Raddatz

T20. The Ventral Hippocampus is Necessary for Trauma Enhanced Aggression (TEA)
Kevin Sattler

T21. Persistent Epigenetic Mediated Paternal Transmission of Stress Phenotypes to Offspring Show Brain Region-Specific Transcriptomic Signature
Ashley Cunningham

POSTER SESSION IV
Tuesday, January 24, 2023
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T22. Modulation of Ventral Pallidum Arkypallidal Neuron Activity by Corticotrophin Releasing Factor (CRF) Signaling
Elizabeth Souter

T23. Connecting -omics Across Tissues in Fragile X Syndrome
Elizabeth McCullagh

T24. Abnormal Ensemble Activity Underlies Pathologic Changes in Social Behavior in Shank3 Mice
Nicholas Frost

T25. Potentiation of the M1 Receptor Exerts Therapeutic Effects in a Mouse Model of Rett Syndrome
Rocco Gogliotti

T26. A Dopamine-Dependent Decrease in Dorsomedial Striatum Direct Pathway Neuronal Activity is Required for Learned Motor Coordination
Stefano Cataldi

T27. Brainwide Mechanisms for Postingestive Learning
Christopher Zimmerman

T28. Differentiating Orbitofrontal Cortex Cell Populations Involved in Actions and Habits
Sophie Yount

T29. Targeting A3 Adenosine Receptor (A3AR) Attenuates Paclitaxel-Induced Cognitive Impairment
Silvia Squillace

T30. Hormonal Control of Dopamine and Reinforcement Learning
Carla Golden

T31. Dopaminergic Contributions to Evaluation and Reevaluation During Neuroeconomic Decision Making
Adrina Kocharian

T32. Spatially and Temporally Selective Dynamics of Striatum-Wide Dopamine Release to Conditioned and Unconditioned Stimuli and Rewards
Mai-Anh Vu

POSTER SESSION IV
Tuesday, January 24, 2023
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T33. Developmental Changes in Medial Prefrontal Cortex Circuitry Contribute to Reduced Adaptive Avoidance Behavior in Adolescent Mice
Caitlin Goodpaster

T34. Insular-Prefrontal Circuit Driving Compassionate Social Behavior
Songjun Li

T35. Transcription Factor 4 Coordinates Developmental and Dopamine-Related Transcriptional Signatures in the Striatum
Nathaniel Robinson

T36. The Nanoscale Organization of Inhibitory Synapses Throughout the Somato-Dendritic Axis
Joshua Garcia

T37. Synaptic Scale Dopamine Disruption in Huntington's Disease Model Mice Imaged With Near Infrared Catecholamine Nanosensors
Sarah Yang

T38. Parkinson's Risk Gene, Synaptojanin1, Regulates Dopamine Transporter Trafficking
Jacqueline Saenz

T39. Locus Coeruleus-Driven BOLD Global Signal Changes in Alzheimer's Rat Model
Nmachi Anumba

T40. Projection-Specific Regulation of Nigrostriatal Dopamine by the Subthalamic Nucleus
Nick Hollon

T41. A Prefrontal to Midbrain Periaqueductal Gray Circuit Restrains Passive Coping Stress Response Patterns
Timothy Skog

T42. Neural Basis of Collective Response to Cold Stress in Social Groups
Tara Raam

T43. Electrochemical-Based Aptamer Sensors for the Real-Time Monitoring of Various Drugs in Brain
Nicole Emmons

POSTER SESSION IV
Tuesday, January 24, 2023
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T44. Unraveling the Complex Effects of Inflammatory Injury on Nociceptive Processing in Spino-Periaqueductal Gray Neural Circuits
Chelsie Brewer

T45. Neuropathic Pain as a Trigger for Histone Modifications in Limbic Circuitry
Svetlana Bryant

T46. Sex Differences in Shock-Elicited Neural Activity in Pain and Fear Networks
Julia Mitchell

Saturday, January 21, 2023

POSTER SESSION I
3:30 PM - 4:30 PM
BALLROOMS 2 & 3

SA1. Interactive Digital Media to Reduce Medical Student Depression and Alcohol Use

*Mary Metcalf, Bradley Tanner**

The impact of chronic stress and vulnerability to substance use disorders is clear. Medical students are subject to a variety of novel stressors as they expand science and clinical skills and experience the unique challenges of providing clinical care – a problem exacerbated during the COVID epidemic response as many took on additional roles. The resulting depression, alcohol abuse, and health impact can establish an ineffective patterns of stress response placing themselves and their future patients at risk. Anticipatory guidance, resilience and student peer support can counter establish alternative coping skills, and decrease negative health outcomes.

With NIAAA funding, we developed a multimodal interactive media toolkit for medical students. An interactive computer simulation, set of self-assessment tools and collection of web-based education modules provide anticipatory and preparatory guidance to the stresses that await them in clinical care. A randomized cross-over study with 63 students played through the simulation and used the interactive media features (ClinicalTrials.gov NCT04494633). The racial and ethnic diversity of the sample of volunteer medical students reflected the current medical student population, and included PGY 1-5 across 16 medical schools.

At baseline we measured Quality of Life (MSQoL), depression (PHS-2), alcohol use, (AUDIT-C, NIDA Quick Screen) and burnout (modified Maslach Burnout Index). 50% of the case group reported unhealthy alcohol use and over 60% of participants met PHQ2 criteria for depression - the control group was similar. Two weeks after the intervention, drug and alcohol use decreased from 50% to 40%, ($p<0.05$). They had similarly decreased depression symptoms from 60% to 40%. All individuals reported a decrease in both substance use and depression. Participants who used the intervention, but not the control group, reported decreased symptoms of burnout, and increase in reported ability to adapt to change.

A brief, multimodal interactive digital intervention can enhance cognitive skills to replace or decrease stress-response coping behaviors associated with substance use and decrease symptoms of depression. Additional investigation of self-directed interventions for medical students is needed. Similar tools may help other healthcare providers.

SA2. Sex-Dependent Features of Oxycodone Self-Administration and Their Ranked Association With Reinstatement of Drug-Seeking in Rats

Gillian Driscoll, Suman Guha, Yanaira Alonso-Caraballo, Jessica Babb, Nick Constantino, Tania Lintz, Elena Chartoff*

A primary barrier to recovery from opioid use disorder (OUD) is relapse. Intravenous self-administration (SA) in rats can model addiction-like behaviors, including escalation of drug intake and reinstatement of drug-seeking after abstinence. In humans, countless factors contribute to OUD development and relapse risk, but how each factor contributes to addiction vulnerability is not understood. Here, we quantified behaviors comprising escalation of oxycodone SA in male and female rats and used partial least squares regression to rank the importance of each measure to the magnitude of cue-induced reinstatement of drug-seeking after 14 days of forced abstinence. Rats were trained to self-administer oxycodone (60 µg/kg/infusion) for 8 days (1 h/d) followed by a 14-d “escalation” period in which oxycodone was available under either short-access (ShA; 1 h/d) or long-access (LgA; 6 h/d) conditions. Separate rats self-administered saline. We found that both sexes escalated oxycodone intake under LgA and ShA conditions, front-loaded drug intake and decreased the latency between oxycodone infusions. In contrast, males, but not females, increased the number of non-reinforced active lever presses over the 14-d escalation period, and females showed greater reinstatement responding than males. We ranked the contribution of these behavioral measures to reinstatement of drug-seeking in a sex-specific manner. The strongest predictor of relapse-like behavior in both sexes was the magnitude of front-loading, but the ranking of the remaining predictors was sex-dependent. Our results demonstrate that behaviors observed during oxycodone SA can be used to predict the magnitude of reinstatement responding in a sex-dependent manner. This raises the possibility that quantifiable behaviors during periods of active drug-taking can predict the risk of relapse in people with OUD.

SA3. Examination of the Role of VTA→IC DA Signaling on Ethanol-Directed Behaviors

Kajol Sontate, Ashmita Mukherjee, Ellie Gilles-Thomas, Sarah Honeycutt, Gregory Loney*

Alcohol-use disorders (AUDs) are characterized by an escalation from moderate, recreational drinking that is goal-directed, to disordered, compulsive drinking that is viewed as habitual. Early in drinking ethanol (EtOH) consumption is dependent on its reinforcing properties thought to be driven by dopamine (DA) release. Conversely, chronic EtOH consumption results in a decrease in evoked DA release from the ventral tegmental area (VTA). The insular cortex (IC) receives dense dopaminergic innervation from VTA and is critically involved in both the processing of the interoceptive properties of EtOH as well as the expression of compulsive-like EtOH consumption. As such, we attempted to manipulate VTA→IC DA neurons and examine multiple EtOH-directed behaviors in Long-Evans rats. Briefly, excitatory and inhibitory DREADDs (or fluorophore control) behind a TH-promoter were expressed in VTA DA neurons and cannulae were inserted in IC to allow for stimulation of IC DA terminals with clozapine-n¬-oxide. Preliminary analyses revealed that activation of VTA→IC DA neurons facilitated acclimatization to EtOH in an intermittent brief-access paradigm. Inhibition of VTA→IC DA release had no effect on established EtOH drinking, but did augment compulsive-like consumption of EtOH that had been adulterated with the bitter tastant quinine. Currently, we are asking if deletion of VTA→IC DA projections will interfere with conditioning with the aversive properties of EtOH in both conditioned taste and place avoidance paradigms. We will employ Cre-dependent viral vectors to drive caspase-3 expression solely in neurons projecting from the VTA to IC prior to place and taste conditioning paradigms. In summary, our preliminary data suggest that insular DA signaling may be critical for relaying the salience of the reinforcing and aversive properties of EtOH. As such, we predict that this pathway may be a key regulator of the development of compulsive-like EtOH consumption.

SA4. Social Interaction Shapes Cocaine Reward and Aversion in Male and Female Rats

Jennifer Wenzel, Erin Foley, Marissa Franco*

A growing body of research shows that social interactions influence motivation for drugs of abuse, drug reinforcement, and relapse. Despite this, investigations into how social interactions shape drug reward and aversion are few. Human and animal studies demonstrate that cocaine (COC) administration produces initial reward which then gives way to dysphoria. Indeed, rats develop a conditioned place preference (CPP) to the immediate effects of COC (0-5 min after administration) and a conditioned place aversion (CPA) to the delayed effects of COC (15 min after). Thus, it is likely that the rewarding and aversive effects of COC contribute to drug taking via positive and negative reinforcement mechanisms, respectively. To assess how social interaction affects COC conditioned reward and aversion we used a place conditioning procedure in which rats learn to associate a unique environment with either the immediate or delayed effects of one of three doses of COC (0.1mg/kg, 0.25mg/kg, and 1.0mg/kg, IV). Further, during each conditioning session, rats were either alone in the environment (as is typical in these procedures) or they were paired with a same-sex cage mate that never received drug. All animals underwent a post-conditioning test. We replicated previous studies showing that 1.0mg/kg COC produces robust CPP and CPA in male rats. In males conditioned alone, 0.25mg/kg COC was unable to produce a CPP, however, in rats conditioned with a conspecific this same dose produced a robust CPP. Further, while 1.0mg/kg COC produced a CPA in males conditioned alone, rats conditioned with a conspecific failed to develop a CPA. As in previous studies using IP COC, female rats developed a CPP at lower doses of COC, and also developed a CPA at lower doses. Like males, the presence of a conspecific during conditioning enhanced drug reward and decreased aversion. Interestingly, conspecifics did not develop a CPP, but did develop a CPA when the drug-treated rat developed a CPA.

SA5. The Role of the Gut-Brain Axis in Intravenous Fentanyl Self-Administration

Michelle Ren, Shahrdad Lotfipour*

The United States is currently experiencing its worst drug crisis, which is largely driven by opioid addiction. The number of drug-related deaths has spiked over the last five years primarily due to fentanyl. It is therefore

necessary to investigate the mechanisms mediating fentanyl's rewarding and reinforcing properties to contribute to the development of successful treatment strategies. Our lab has developed a rat model of fentanyl intravenous self-administration (IVSA) to investigate factors that influence fentanyl intake, including sex, drug dose, and gut bacteria. Gut bacteria communicate with the brain, and vice versa, via the gut-brain axis to regulate brain function, mood, and behavior. Preclinical research has shown a significant impact of the intestinal microbiota on regulating addiction-related behaviors. We show that male and female Sprague Dawley adult rats learn response requirements via reinforced nose pokes to acquire fentanyl infusions at 0, 1.25, or 2.5 µg/kg/infusion on an escalating schedule of reinforcement. Our data show the impact of fentanyl IVSA on gut microbiota diversity in wild-type Sprague Dawley rats in a sex- and dose-dependent manner. Additionally, we found that antibiotic treatment depletes gut bacteria and enhances fentanyl self-administration in males and females. Our findings provide feasibility for an intravenous fentanyl self-administration animal model and highlight an important relationship between knockdown of gut bacteria and fentanyl self-administration in adult rats, which provides support for a significant relationship between the gut microbiome and opioid use. Further work in this field may lead to effective, targeted treatment interventions in opioid-related disorders.

SA6. Chronic Intermittent Ethanol Drinking Alters Brain Endocannabinoid System and Cannabinoid Receptor Neutral Antagonism Decreases Drinking

Russell Dulman, Huaibo Zhang, KY Vinod, Subhash Pandey*

The endocannabinoid system is intriguing for developing new treatments for addictive disorders. Cannabinoid-1 receptor (CB1) antagonists reduce drug consumption in rodents, but CB1 inverse agonist rimonabant caused psychiatric side effects in humans. Neutral CB1 antagonists may reduce drug consumption without side effects. We tested CB1 neutral antagonist AM4113 (1mg/kg, i.p.) for effects on intermittent ethanol (20%) drinking and sucrose (2%) drinking in male C57 mice and examined endocannabinoid system gene expression to assess effects of chronic ethanol in addiction-related brain regions. Mice drank average ethanol 22.4 g/kg/day (baseline, n=12). AM4113 treatment reduced consumption to 11.1 g/kg/day versus baseline ($p<0.001$) and also compared to post-treatment vehicle 17.5 g/kg/day ($p=0.012$, n=6 per group). AM4113 treatment didn't alter total fluid intake, body weight, or water drinking during non-ethanol- access days. In another cohort, AM4113 treatment didn't affect sucrose drinking versus

vehicle (p=0.627, n=6 per group). In a third cohort, ethanol drinking increased CB1 receptor mRNA expression in the dorsal hippocampus and prefrontal cortex compared to water-drinking controls (n=12 per group, p=0.016 and p=0.036) without significant changes in CB1 expression in the ventral hippocampus or amygdala. In the amygdala, however, ethanol drinking decreased expression of key endocannabinoid biosynthethic enzyme diacylglycerol lipase (DAGL) (p=0.018). Chronic ethanol drinking had no other significant effects on gene expression of other endocannabinoid enzymes in these brain areas. Overall, AM4113 reduces chronic ethanol drinking without anhedonic or metabolic consequences. Furthermore, systemic AM4113 treatment may reduce drinking through a dorsal hippocampal or prefrontal cortical mechanism as ethanol elevates CB1 receptor expression there. These findings suggest cannabinoid receptor signaling is enticing research avenue for alcohol use disorder pharmacotherapy.

SA7. Sex Differences in the Impact of Electronic Nicotine Vapor on Corticotropin-Releasing Factor Receptor 1 Neurons in the Mouse Ventral Tegmental Area

ManHua Zhu, Melissa Herman*

Nicotine engages dopamine neurons in the ventral tegmental area (VTA) to encode reward and drive the development of nicotine addiction, however how nicotine selectively alters other VTA populations remains to be determined. Here, we used male and female CRF1-GFP mice and nicotine vapor exposure to examine the effects of nicotine in VTA corticotropin-releasing factor receptor 1 (CRF1) neurons from naïve mice and mice exposed to acute (3-sec vapor delivered every 10 mins over a 3-hr session) and chronic (28 days of daily 3-hr sessions) nicotine vapor. We used immunohistochemistry and electrophysiology to examine neuronal activity, excitability, and inhibitory signaling. We found that VTA CRF1 neurons are mainly dopaminergic and project to the nucleus accumbens (VTA-NAcCRF1 neurons). VTA-NAcCRF1 neurons displayed greater phasic inhibition in naïve females and greater focal nicotine-induced increases in firing in naïve males. Following acute nicotine vapor exposure, phasic inhibition was not altered, but focal nicotine-induced tonic inhibition was enhanced in females and diminished in males. Acute nicotine vapor exposure did not affect firing in VTA-NAcCRF1 neurons, but females showed lower baseline firing and higher focal nicotine-induced firing. Activity (cFos) was increased in the CRF1 dopaminergic VTA population in both sexes, but with greater

increases in females. Following chronic nicotine vapor exposure, both sexes displayed reduced basal phasic inhibition and the sex difference in tonic inhibition following acute vapor exposure was no longer observed. Additionally, activity of the CRF1 dopaminergic VTA population was no longer elevated in either sex. These findings reveal sex- and exposure-dependent changes in mesolimbic VTA-NAc CRF1 neuronal activity, inhibitory signaling, and nicotine sensitivity following nicotine vapor exposure. These changes potentially contribute to nicotine-dependent behaviors and the intersection between stress, anxiety, and addiction.

SA8. Genetic Variation Influences on Learning, Memory and Alcohol Metabolism

Laurel Seemiller, Lisa Goldberg, Prescilla Garcia-Trevizo, Thomas Gould*

Ethanol impairs learning and memory, and adolescents could be uniquely susceptible to these effects. Additionally, genetic background may play an important role in the effects of alcohol on learning and memory processes as well as metabolic pathways. Here, we examine the impact of genetic background on learning and memory as well as determining blood ethanol concentrations (BECs) in an inbred strain panel. Male and female adolescent C57BL/6J, C57BL/6NJ, DBA2/J, 129S1/SvImJ, A/J, BALB/cByJ, BTBR T+ tf/J, C3H/HeJ, and FVB/NJ were administered with saline or alcohol 15 minutes prior fear conditioning training, where they received 2 conditioned stimulus (CS)-footshock (US; 0.45 mA) pairings. One day after, animals were returned to training chambers for context freezing and on new chambers for cued testing. Freezing behavior was scored and analyzed. After behavior testing, animals on the saline treated fear conditioning group were treated with an acute ethanol dose (1.5 g/kg, i.p.) and BEC was measured 15 minutes later. To assess genetic variation of relevant alcohol- and learning-relevant genes we conducted a SNP query for genes: Adh4, Adh1, ApoE, ApoB, Gabra1, Gabra2, Gabra3, Dlg3, Alcp1, Alcp3, Dlg2, Chrna7. Variant Effect Predictor (VEP) was used in 2 SNPs found in C57BL/6NJ these SNPs differed from C57BL/6J, and determined its consequence on sequence regulation. We found that contextual learning deficits vary across inbred strains after acute ethanol exposure. Furthermore, we did not see BEC differences between the strains, suggesting that alcohol-metabolism may not entirely be associated with the learning deficits seen. SNP query revealed large differences in variation when comparing C57BL/6J mice with the other strains and focused on 2 variants seen in C57BL/6NJ strain that differs very little in genetic background. Those variants seen in ApoB and Chrna7 were primarily characterized affecting regulatory sequences of the genes. Future studies

will include how those variants inform to learning deficits seen in a fear conditioning paradigm.

SA9. Chronic Alcohol Exposure Disrupts Orbitofrontal-Premotor Circuit Transmission of Action-Related Information

Christina Gremel, Andrew Wright, Christian Cazares, Natalie Paredes, Yuewen Wang, Tianyu Wang, Amia Loveless*

Alcohol Use Disorder (AUD) disrupts action control processes important for decision-making. Aberrant activity in posterior premotor cortex (M2) has been implicated in compulsive action control and observed in those with AUD. We have recently shown using an animal model of chronic alcohol exposure that M2 hyperactivity is in part responsible for disrupted action control. However, M2 does not act alone and whether upstream regions conveying action information also show disruption that contributes to dysfunctional decision-making is not clear. Lateral orbitofrontal cortex (lOFC) is a source of afferents into M2 and lOFC activity is important for encoding action information. LOFC activity is also disrupted in those with AUD. In animals, chronic alcohol exposure leads to increased lOFC activity during actions, raising the hypothesis that aberrant lOFC-M2 transmission may contribute to disrupted action control. Here, we used a self-paced lever-press hold down task in which mice rely on prior action-related experiences to guide subsequent action performance. We show that OFC-M2 afferents functionally contribute to action information and that their terminal activity differentially instantiates current and prior action information during ongoing action execution. Chronic alcohol exposure results in long-lasting changes to lOFC-M2 terminal activity during decision-making and preliminary findings from ex vivo whole-cell physiology studies suggest a concurrent decrease in transmission from OFC terminals onto M2 projection neurons. Ongoing experiments are examining whether chronic chemogenetic manipulations of OFC-M2 afferent activity can restore use of lOFC-based information. Our results thus far identify a novel circuit for cortico-cortical integration and transmission of action-related information that is disrupted following chronic alcohol exposure.

SA10. Changes in Striatal Dopamine Release, Sleep, and Behavior During Spontaneous Δ-9-Tetrahydrocannabinol Abstinence in Male and Female Mice

Andrew Kesner, Yolanda Mateo, Stephanie Ramos-Maciel, Nina Westcott, Hartley Carlson, David Lovinger*

Withdrawal symptoms are observed upon cessation of cannabis use in humans. Although animal studies have examined withdrawal symptoms following exposure to delta-9-tetrahydrocannabinol (THC), difficulties in obtaining objective measures of spontaneous withdrawal using paradigms that mimic cessation of use in humans have slowed research. The neuromodulator dopamine (DA) is affected by chronic THC treatment and plays a role in many behaviors related to human THC withdrawal symptoms. These symptoms include sleep disturbances that often drive relapse, and emotional behaviors like irritability and anhedonia. We examined THC withdrawal-induced changes in striatal DA release and the extent to which sleep disruption and behavioral maladaptation manifest during abstinence in a mouse model of chronic THC exposure. Using a THC treatment regimen known to produce tolerance, we measured electrically elicited DA release in acute brain slices from different striatal subregions during early and late THC abstinence. Long-term polysomnographic recordings from mice were used to assess vigilance state and sleep architecture before, during, and after THC treatment. We additionally assessed how behaviors that model human withdrawal symptoms are altered by chronic THC treatment in early and late abstinence. We detected altered striatal DA release, sleep disturbances that mimic clinical observations, and behavioral maladaptation in mice following tolerance to THC. Altered striatal DA release, sleep, and affect-related behaviors associated with spontaneous THC abstinence were more consistently observed in male mice. These findings provide a foundation for preclinical study of directly translatable non-precipitated THC withdrawal symptoms and the neural mechanisms that affect them.

SA11. Morphine's Opposing Actions Define Opioid Preference Versus Seeking

*Mao Ye, Sukjae Kang, Shijia Liu, Lanling Jia, Jinho Jhang, Sung Han**

Opioids are highly addictive because they drive intense pleasure and a craving for continued use. It has been suggested that opioid-induced positive affect and craving are mediated by discrete neural mechanisms1-4. However, little is known about how opioids differentially mediate these distinct Responses. Here, we report that discrete subpopulations of μ-opioid receptor-expressing neurons in the lateral parabrachial nucleus (Oprm1PBL) mediate different morphine-induced adaptive behaviors by responding to morphine in opposite ways. Oprm1PBL neurons in the external lateral subdivision that project to the central amygdala (Oprm1PBel→CeA) are inhibited by morphine and mediate morphine-conditioned place preference

(i.e., positive affect), whereas Oprm1PBL neurons in the dorsal lateral subdivision that project to the ventral tegmental area (Oprm1PBdl→VTA) are activated by morphine and mediate morphine-induced hyperlocomotion and drug-seeking behaviors (i.e., craving). Oprm1PBdl→VTA neurons form glutamatergic synapses onto VTA dopaminergic neurons, and these synapses are potentiated by repeated morphine exposure. Surprisingly, optogenetic stimulation of Oprm1PBdl→VTA neurons induced a dramatic dopamine surge in the nucleus accumbens (NAc). Synaptic depotentiation or chemogenetic inhibition of this pathway completely blocked cue-induced drug-seeking behavior, suggesting that Oprm1PBdl→VTA excitatory inputs mediate opioid craving. These results provide novel circuit-based insights into opioid modes of action, creating critical stepping stones for treating opioid addiction and developing safe analgesics.

SA12. Individual Differences in Susceptibility to Postpartum Mood Changes and Underlying Neuroimmune and Resting State Neural Connectivity in Sprague Dawley Rats

Janace Gifford, Jaclyn Schwarz*

Approximately 60% of new mothers experience postpartum mood disturbances known as the “baby blues.” Fortunately, most new mothers recover within a few weeks but a significant subset (10-15%) go on to develop postpartum depression (PPD). The present study aimed to examine the onset of anhedonia and associated changes in neuroimmune and endocrine function as well as altered resting state brain function postpartum. First time dams underwent a series of sucrose preference tests (prior to breeding and postpartum) to examine depressive-like behavior. Previous data revealed pre-pregnancy, most rats exhibit a strong sucrose preference (>80%) but immediately postpartum approximately 40% of new mothers display anhedonia suggesting some mothers are susceptible and others resilient to this onset of postpartum anhedonia. To better understand these individual differences, brain tissue was collected from animals at either postnatal day 2 or 9 and assessed for neuroimmune function. Fecal samples were also collected and assayed for estradiol and corticosterone levels. Results indicated an increase in IL-6 in susceptible animals in the dorsal hippocampus and medial prefrontal cortex (mPFC) at P2 and P9 time points as well as decreased BDNF in the mPFC at P2 and P9. Increased corticosterone postpartum was observed in resilient animals while no differences were observed in estradiol. Further, results suggest susceptible animals have altered default mode network

integration between P3 and P10. Overall, this work aims to better understand and predict susceptibility or resiliency to postpartum anhedonia with hopes to proactively identify risk factors associated with PPD to aid in the development of future targeted therapeutics. Funded by R21MH122862 to JMS.

SA13. The Expression of Key Hub Genes Within the Nucleus Accumbens Mediates Resilience to Chronic Stress

Trevonn Gyles, Eric Parise, Arthur Godino, Eric J. Nestler*

Major depressive disorder (MDD) is the leading cause of disability and a leading contributor to suicide according to the World Health Organization. Unfortunately, close to half of all patients diagnosed with MDD are at least partly resistant to antidepressant treatment. Notably, both genetic and environmental factors, including exposure to chronic social stress, play a role in the development of MDD and related syndromes. The chronic social defeat stress (CSDS) paradigm in mice has proven to be a highly useful animal model for studying depression-related behavioral abnormalities. Importantly, this paradigm allows for the identification of animals that succumb to the effects of the stress, termed susceptible, from those that do not, termed resilient. To better understand the potential genes underlying the resilient phenotype, we performed RNA-sequencing on mice exposed to CSDS and compared gene expression changes within the nucleus accumbens (NAc) between resilient and susceptible mice. Using weighted gene co-expression network analysis (WGCNA), we identified gene expression patterns that are associated uniquely with resilience. These data were then evaluated using an undirected key driver analysis that allows for the reconstruction of accurate cellular networks (ARACNE) based on gene-gene correlations. We identified three genes (Gprin1, Bcr, and Stx1a) that were predicted to be key drivers (predicted to regulate other genes) within a highly significant, resilient-specific module. We are now investigating how changes in the expression of these genes could lead to changes in depressive-like behavior. To test this, multiple cohorts of mice were exposed to CSDS or another stress paradigm, chronic variable stress, and mRNA expression levels of these target genes were assessed. We also tested the functional consequences of virally manipulating these genes following prior to CSDS. Evidence from these studies suggests that overexpression of each of these genes in NAc neurons produces a pro-resilient effect. Current work is investigating these molecular mechanisms in a cell-type-specific manner within the NAc. Together, these studies are providing novel insight into the molecular basis of stress resilience.

SA14. A Characterization of Social Defeat Stress and its Impacts on Depressive-Like Behavior in Rats

Sara Pickernell, Sparsha Muralidhara, Paige Sidwell, Grace Hey, Darragh P. Devine*

Major depressive disorder (MDD) is characterized by persistent and prolonged despair and anhedonia. It is well-established that social stressors play an important role in the etiology of MDD. Accordingly, social stress has been modeled in preclinical studies using the social defeat model in rodents. Patterns of dominant and submissive behaviors have been examined across repeated training and testing days in mice, but not yet in rats. We are investigating the changes in dominance and submissive behaviors in both the resident and intruder rats across time, including potential correlations between the submissive behaviors in the intruders, and the intensity of dominance exhibited by the residents. Most measures of dominance behavior, latency to attack, and social interaction did not change across 8 daily social defeat training sessions. However, the total time residents spent pursuing the intruder rats significantly decreased across training and the introduction of a novel defeat-naive intruder was associated with greater resident pin latencies. This may indicate increased submissive behavior by intruders across training days. After 6 daily social defeat sessions, intruder rats' social interactions and engagements with physical stimuli were assessed in a novel complex environment. Socially stressed rats interacted with the environmental stimuli less than the unstressed control rats. The stressed group displayed greater prosocial, aggressive, and submissive behavior with conspecifics compared to the control rats. Additionally, we assessed correlations between depression-related behavior and physiological biomarkers in the stressed and control rats when exposed to the mild stressor of a novel circular corridor task. We found no significant differences in distance locomoted in the task or in the thymus and adrenal weights between the groups. The socially stressed group displayed significantly greater plasma corticosterone levels compared with the control group.

SA15. Characterization of Endogenous Opioid Systems Within the Paraventricular Nucleus of the Thalamus

*Sofia Shirley**

The paraventricular nucleus of the thalamus (PVT) is a stress-sensitive region of the brain that regulates emotional and motivational processes. Recent studies demonstrate that the PVT is a heterogenous structure

composed of molecularly distinct neuronal types that are distributed along its antero-posterior axis. These molecularly defined PVT cell types are embedded within divergent projections to various limbic regions, such as the nucleus accumbens (NAc), central nucleus of the amygdala (CeA), and medial prefrontal cortex (mPFC). Moreover, the heterogenous composition of the PVT is functionally relevant because different subregions and cell types of the PVT have been linked to diverse behavioral outcomes. The kappa opioid receptor (KOR) is expressed throughout the PVT and has been shown to play important roles in mediating anxiety-like behavior. Additionally, the mu opioid receptor (MOR) is also expressed throughout the PVT and is established to promote euphoric emotional states. These two receptors are involved in modulating affective states, however it is currently unclear how endogenous opioids are integrated into heterogenous PVT circuits. Here I used whole cell patch clamp electrophysiology to investigate the responsivity of PVT neurons to kappa (KOR) and mu opioid receptor (MOR) activation along the antero-posterior axis of the PVT. I found that KOR and MOR activation elicits inhibitory currents in PVT cells, which provides a mechanism by which KOR and MOR regulate PVT neural activity. Further, somatodendritic KOR and MOR inhibit PVT neurons projecting to the NAc and mPFC. On-going work is aimed at identifying if somatodendritic KOR and MOR differ based on molecular identity, electrophysiological properties, and/or projections of PVT cells. This work will provide a framework for our lab to further dissect the role of PVT opioid systems in mediating stress-related behaviors and affect. Understanding these PVT opioid systems will inform us of the mechanisms underlying emotional behavior and can provide insight into how these systems are disrupted in anxiety and psychological disorders.

SA16. Sex-Specific Effects of Psychedelic Drug Exposure on Central Amygdala Reactivity and Behavioral Responding

Devin Effinger, Sema Quadir, Maria Ramage, Meredith Cone, Melissa Herman*

Psilocybin, and its active metabolite psilocin, have been shown to elicit rapid and long-lasting symptom improvements in a variety of affective psychiatric illnesses. However, the region-specific alterations underlying these therapeutic effects remain unclear. We previously demonstrated that a single administration of psilocin produced sex-and time-specific changes in central amygdala (CeA) reactivity to an aversive air puff stimulus in male and female rats. Here, we investigated sex differences in stimulus-locked behavioral responding and the association of psilocin-induced changes in

CeA reactivity with sex-specific changes in behavioral responding. We found no differences in locomotion or exploratory behavior in either sex after psilocin (2 mg/kg, s.c.), however we did observe sex-specific differences in stimulus-locked threat responding. Consistent with previous reports, we found that females primarily displayed active coping responses (i.e., darting) and that these responses were unaffected by psilocin administration. In contrast, males displayed both active (darting) and passive (immobility) coping responses and there were significant reductions in CeA reactivity specific to the psilocin-treated males employing an active threat response ($F_{Treatment(4,16)}=6.566$, $p=0.003$). To examine basal changes in activity with psilocin administration, we performed immunohistochemical analysis of the activity marker, c-Fos, and found significant increases in specific CeA sub-regions following acute psilocin administration. This study provides new evidence that a single dose of psilocin produces sex- and time-dependent changes in basal CeA activity, behavioral responding, and CeA reactivity. Additionally, we show that these changes in CeA reactivity may be driven by specific CeA sub-populations and may correlate to threat responding strategies in males. Future work will explore potential circuit-based alterations underlying observed changes in CeA activity and reactivity.

SA17. Studying the Impact of Shank3-Deficiency on the Mesoaccumbens Pathway of Reward

Marie Barbier, Keerthi Thirtamara Rajamani, Shai Netser, Shlomo Wagner, Hala Harony-Nicolas*

Social deficits are a core symptom of autism spectrum disorder (ASD). Clinical studies have implicated the mesoaccumbens reward circuit in autism spectrum disorder. However, the causality between alterations in this system and social deficits has not been established. The ventral tegmental area (VTA), a core node of the mesolimbic pathway, is interconnected with the nucleus accumbens (NAc) via the VTA dopaminergic projections. Despite the role of the reward system in social interaction, little is known about the impact of ASD associated mutations on processing social reward and on the functional integrity of this pathway. In this work, we study the effect of a mutation in an ASD high-risk gene, Shank3, on the mesoaccumbens pathway in rats. We hypothesize that Shank3 mutation impacts neural activity in the mesoaccumbens pathway, causing abnormalities in accumbal dopamine transmission and leading to impairments in processing social reward. To identify abnormalities in dopamine transmission in Shank3-deficient rats that correlate with deficits

in processing social reward, we used fiber photometry to record in the VTA in combination with a dopamine sensor in the NAc during a social reward paradigm (n = 15 per genotype, WT, HET and Shank3-KO; and for the behavioral experiment, n = 40 per genotype). In this paradigm we introduced two rewarding stimuli, social and food, during satiety and food deprivation and examined investigation time for each reward during the two conditions ($p < 0.001$ between WT and Shank3-KO at food deprivation). To control for attentional deficits, we used the same paradigm, but replaced the social stimuli with a moving toy rat (behavioral experiment, n = 30 per genotype). To rule out reduced motivation to food or impairment in food consumption, we assessed food consumption (n = 20 per genotype). We found that Shank3-deficient rats have deficits in processing reward that are associated with perturbation in VTA neural activity and an intact attention and food consumption. Our study demonstrates that Shank3-deficient rats have deficit in processing reward and provides a first step toward understanding the role of Shank3 in the reward system, and how Shank3-deficiency may lead to social deficits.

SA18. Modulation of Potassium Channels Preserves Temporal Fidelity in Sensory Processing

*Leonard Kaczmarek**

Potassium channels in auditory neurons are rapidly modified by changes in the auditory environment. In response to elevated auditory stimulation, short-term mechanisms such as protein phosphorylation and long-term mechanisms linked to channel synthesis increase the activity of channels that promote high frequency firing. We have now used simple simulations of cochlear hair cells and postsynaptic neurons to demonstrate that the amplitudes of potassium currents in neurons required for optimal encoding of a low-level auditory signal differs substantially from that for louder sounds. Specifically, the cross correlation of the output of a neuron with an auditory stimulus is increased by increasing potassium currents as sound amplitude increases. Although it has been suggested that channel modulation allows neurons to fire at high rates in response to high sound levels, we found that the cross correlation is entirely independent of firing rate and that combinations of currents that maximize firing to a stimulus provide very poor temporal fidelity. We also found that levels of potassium currents that maximize the temporal fidelity of the output of an ensemble of thirty neurons differ from those that maximize temporal fidelity for a single neuron. This suggests that, to maximize preservation of temporal information, modulatory mechanisms must coordinate channel activity in

groups of neurons receiving similar synaptic inputs. The simulations provide an explanation for the modulation of the intrinsic excitability of auditory brainstem neurons by changes in environmental sound levels, and the results may extend to information processing in other neural systems.

SA19. Distinct Dopamine Signaling in Action Sequence Learning Driven by Reward Predictive Stimulus

Robin Magnard, Yifeng Cheng, Joanna Zhou, Laia Castell, Patricia Janak, Youna Vandaele*

Dopamine (DA) acts as a teaching signal in reinforcement learning through reward prediction errors. Yet, our comprehension of DA role's in sequence learning task is still incomplete. Here we studied DA dynamics during action sequence learning focusing on the development of automaticity. We tested male and female rats in two instrumental procedures, the lever insertion fixed-ratio 5 (LI5) task and the lever retraction fixed-ratio 5 (LR5) task, where the lever either serves as the distal cue that triggers the initiation of a chain of actions or as the proximal cue that signals sequence completion and sucrose delivery, respectively. We recorded DA neuron activity and DA release via fiber photometry imaging. TH-Cre or WT rats were respectively infused into the VTA or NAc Core with a Cre-dependent GCaMP6f or dlight 1.2 virus and monitored while performing the LR5 or LI5 task. We found substantial task differences with no effect of sex. In the LR5 task we saw automaticity, behavioral chunking and a relative inflexible behavior. In contrast, in the LI5 task, behavior was more flexible and goal directed. We monitored distinct changes in DA signaling, but GCaMP and dlight-mediated signals in the VTA or in the NAc core were similar to each other. In the LR5 task, we found a rapid shift in the activation of DA neurons from reward retrieval to the earlier LR cue, followed by a decrease in cue-evoked DA neuron activity across repeated trials as learning elaborates. In contrast, in the LI5 task, cue- and reward-induced DA activation remained relatively constant across trials and sessions. Contingency degradation tests displayed the opposite pattern, with a dip in DA neuron activity after unrewarded sequence completion in LI5 task but a blunted activity in LR5 task. These results show task differences in DA signaling that may correspond to degree of behavioral automaticity and help delineate dopaminergic correlates of action sequence learning in response to reward predictive cues.

SA20. Ventral Tegmental Area Release of Glutamate or GABA From Local Neurons Play Distinct Roles in Aversion, Reward and Feeding Behavior

Huiling Wang, Flavia Barbano-Soria, Shiliang Zhang, Jesse Torija Maximo, Rucha Kulkarni, Bing Liu, Marisela Morales*

The ventral tegmental area (VTA) contains dopamine neurons intermixed with GABA neurons (expressing vesicular GABA transporters,VGaT), glutamate neurons (expressing vesicular glutamate transporters type 2, VGluT2), and combinatorial glutamate-GABA neurons co-expressing VGluT2 and VGaT. The role of VTA-VGluT2 and VTA-VGaT neurons in behavior has been examined in single recombinase expressing transgenic mice, but these mice are not suitable for the selective tagging of dual VGluT2-VGaT, VGluT2-only or VGaT-only neurons. We generated a double vglut2-Cre/vgat-Flp transgenic mouse and by VTA injection of INTRSECT adeno associated viral vectors (Con-Foff, Coff-Fon or Con-Fon) induced expression of channelrhodopsin in VTA-VGluT2-only, VTA-VGaT-only, or VGluT2-VGaT neurons. By VTA quantitative ultrastructural analysis, we found that local VGluT2-only and local VGaT-only neurons established multiple synapses on VTA neurons, but local dual VGluT2-VGaT neurons infrequently established synapses. These findings indicate that VTA release of glutamate or GABA is provided mostly from glutamate-only or GABA-only neurons. By behavior testing, we found that VTA-glutamate release from local glutamate-only neurons, but not from glutamate-GABA neurons, is rewarding, and that VTA-GABA release from local GABA-only neurons, but not from glutamate-GABA neurons is aversive. Next, we determined the extent to which VTA release of glutamate or GABA from local neurons play a role in food reward. We found that (1) VTA-glutamate release from local glutamate-only neurons decreases feeding behavior, (2) VTA release of glutamate or GABA from local glutamate-only, GABA-only, or dual glutamate-GABA neurons negatively affects learning to obtain food reward, and (3) an unanticipated role of VTA release of glutamate or GABA impairing cue-induced reinstatement of food-seeking behavior. In summary, we demonstrated that VTA release of glutamate or GABA from local glutamate-only or GABA-only neurons have major opposite (reward vs aversion) or common effects on specific food reward behaviors, contrasting with VTA release of glutamate and GABA from local dual glutamate-GABA neurons, which has just a partial effect in the learning of an instrumental task to obtain food reward.

SA21. Sleep Deprivation Decreases Dendritic Spines and Expression of CaMKIIα and SST in Hippocampal Neurons Following Contextual Fear Learning

*Matthew Tennin, Jake Valeri, Rita Lacy, Harry Pantazopoulos, Barbara Gisabella**

Recent studies suggest that specific subsets of dendritic spines are increased during sleep in selective neurons involved in recent learning. However, information regarding the neuronal populations and involved in dendritic spine changes during sleep in specific memory circuits is limited. CaMKIIα, a marker for excitatory neurons involved in contextual fear memory, is a promising candidate. Recent studies also suggest that somatostatin (SST) plays a role in fear memory consolidation during sleep. We tested the hypothesis that dendritic spines in a recent fear memory trace are upscaled during sleep in the presence of broad downscaling, and that these neurons co-localize with either SST or CaMKIIα.
We used ArcCreERT2 mice to label neurons that encode fear memory combined with dual AAV viral vector labeling of dendritic spines to label Arc positive (Arc+) and Arc negative (Arc-) neurons. Dendritic branches were sampled using confocal imaging, and spine densities were quantified using 3D image analysis from sleep deprived (SD) and control mice (n=6/group). We used immunofluorescence and microscopy to quantify neurons labeled with CaMKIIα and SST with and without ARC, to examine neuronal populations involved in fear memory specific alterations in SD mice.
We observed an overall decrease of dendritic spine density in SD mice selectively in mushroom spines ($p<0.006$). Arc+ dendrites showed no overall difference in spine density. However, mushroom spines in Arc+ branches showed the largest decreased density in SD mice ($p<0.0003$), indicating that upscaling of mushroom spines during sleep is driven by neurons that encoded the recent contextual fear memory. Furthermore, we observed that a large percentage of Arc+ neurons colocalized with CaMKIIα, and a small percentage co-localized with SST. Arc-CaMKIIα neurons were significantly decreased in sector CA1 of the hippocampus ($p<0.03$), and Arc negative SST neurons were significantly decreased in CA1 ($p<0.01$) and CA4 ($p<0.05$) of SD mice.
Our findings indicate that sleep contributes to increases in dendritic spines primarily driven by mushroom spines in CaMKIIα neurons that recently encoded fear memory. Our observed changes in SST neurons that did not encode fear memory suggests these neurons may participate in regulating activity of excitatory neurons during sleep

SA22. Delineation of the G Protein-Coupled Receptor Kinase Phosphorylation Sites Within the D1 Dopamine Receptor and How They Regulate Receptor Function

David Sibley, Amy E. Moritz, Nora Madaras, Michele L. Rankin, R. Benjamin Free, Raphael Haider, Julia Drube, Arun K. Ghosh, John J.G. Tesmer, Carsten Hoffmann*

Dopamine receptors (DRs) regulate diverse physiological functions including movement, cognition, mood, and reward-related behaviors, and are involved in the etiology and/or therapy of numerous neuropsychiatric disorders. The D1-like DRs (D1R and D5R) increase cAMP levels, while the D2-like DRs (D2R, D3R, D4R) decrease cAMP levels. All DRs also recruit β-arrestin which activates distinct signaling cascades, and also initiates receptor desensitization and internalization. The desensitization process is intimately linked with receptor phosphorylation by G protein-coupled receptor kinases (GRKs). The D1R possesses 32 intracellular serine and threonine residues and is known to be phosphorylated by several kinases including protein kinase A (PKA), protein kinase C (PKC), and several GRKs. Using mutational analyses, we previously identified the PKA- and PKC-mediated phosphorylation sites and showed that GRK4 constitutively phosphorylates the receptor. We have now identified the residues that are phosphorylated by GRKs in response to DA activation of the D1R. We found that this phosphorylation involves serine and threonine residues on the C-terminus and ICL3 of the D1R. Mutation of these residues severely impairs β-arrestin recruitment, but causes little effect on G protein-mediated signaling. Our results also indicate that most of the DA-induced GRK phosphorylation occurs on residues T360 and S362 in the proximal C-terminus, and that these residues are responsible for β-arrestin recruitment to the D1R. Notably, GRK2/3 appear not to be involved in β-arrestin recruitment to the D1R, as treatment with GRK2/3-selective inhibitors had no effect on this process. We found similar results using HEK293 cells in which the endogenous GRKs were individually, or combinatorially, knocked out via CRISPR. For instance, DA-induced β-arrestin recruitment to the D1R was not impaired in dual GRK2/3 KO cells whereas β-arrestin recruitment to the D2R was attenuated in these cells. In contrast, DAinduced β-arrestin recruitment to the D1R was significantly impaired in dual GRK5/6 KO cells. We are currently using GRK5/6-selective inhibitors to determine if they mimic the effects observed with the GRK5/6 KO cells. Overall, these results suggest that GRK5/6 are involved in DA-induced β-arrestin recruitment to the D1R.

SA23. Single Channel Characteristics of Conductance and Non-Conductance Modifying Allosteric Modulators of the NMDA Receptor at the Channel Gate

Elijah Ullman, Riley Perszyk, Jing Zhang, Russell Fritzemeier, Nicholas Akins, Dennis Liotta, Stephen Traynelis*

The N-methyl-D-aspartate receptor (NMDAR) is a ligand gated ion channel that is permeable to Na+ and Ca2+ and mediates a slow component of excitatory neurotransmission. NMDARs are implicated in synaptic plasticity and disease states such as in Parkinson's, Alzheimer's, schizophrenia, and stroke. Here we have evaluated the characteristics at the single channel level of five series of allosteric modulators with structural determinants of bindings in regions that constitute the NMDAR channel gate. We have generated two series of positive allosteric modulators (PAMs), EU1622 and EU1794 which generate two and three subconductance states respectively, and reduce the Ca2+:Na+ permeability ratio (Perszyk et al., 2018, 2020). Although the mechanism underlying the conductance-reduction of these two series are unknown and under active investigation, we compare properties of conductance-modifying and non-conductance modifying allosteric modulators such as open probability, conductance, mean open time, deactivation time course, and agonist potency. Reduction of calcium permeability represent interesting clinical potential due to potentially reduced neurotoxicity compared to non-conductance modifying modulators.

SA24. RNA Binding Proteins are Enriched in Tau Interactions and Dysregulated Across Tauopathy

Tomas Kavanagh, Aditi Halder, Glenda Halliday, Eleanor Drummond*

Tau aggregation is the hallmark pathology of many neurodegenerative diseases – termed tauopathies. In each tauopathy, tau aggregates have unique isoforms, composition, structure, and location in the brain. How tau drives these different diseases remains unknown. Interactome studies are a powerful tool to understand tau-mediated disease mechanisms. Therefore, we collated all tau interactome data from human (post-mortem brain and cell models, 7 studies) and rodent (5 studies) to identify the proteins most consistently interacting with tau. We identified 2,084 proteins that interact with tau in human studies and 1,152 that interact with tau in rodent models. Some of the most prolific tau interactors were RNA binding proteins and specifically HNRNPA1, HNRNPA2B1 and HNRNPK are the most consistent tau interactors (GO-Enrichment: RNA Binding FDR = 2.29*10^-102, 4/7 studies). To determine how these hnRNPs interact with tau we performed a large

immunohistochemistry study examining the relationship between hnRNP expression and tau pathology in the frontal cortex and hippocampus across 7 conditions: Alzheimer's disease, corticobasal degeneration, primary age related tauopathy, Pick's disease, progressive supranuclear palsy, mild cognitive impairment, and control cases. Secondly, we assessed if HNRNP puncta were colocalising with common cellular compartments including stress granules or the lysosome. Surprisingly, we observed no colocalization between large, phosphorylated tau aggregates and any hnRNP across each tauopathy. However, mislocalization and disease specific changes in hnRNP expression were observed and the pattern of hnRNP dysregulation coincided with tau isoform enrichments in disease. Furthermore, we observed an increase in expression of hnRNPs in glia in the frontal cortex. In conclusion, hnRNPs are not present in large tau aggregates but are likely early disease-associated tau interactors which may have a role in driving early tau pathology.

SA25. High Levels of Cell-Free Mitochondrial DNA Deletions in Cerebrospinal Fluid From Patients With Idiopathic, But Not LRRK2, Parkinson's Disease

*Margalida Puigros, Anna Calderon, Alexandra Pérez-Soriano, Cristina De Dios, Manel Fernández, Anna Colell, Maria-José Martí, Eduard Tolosa, Ramon Trullas**

The etiology of the majority of cases of Parkinson's disease (PD) is still unknown and classified as idiopathic (iPD). Pathogenic mutations in single nuclear genes, such as LRRK2, cause genetic forms of PD in a small fraction of total disease cases. Remarkably, mitochondrial dysfunction underlies both idiopathic and genetic forms of PD. The mitochondrial DNA genome (mtDNA) is a key regulator of mitochondrial function. Deletions of the human mtDNA genome accumulate during normal aging. The most frequent mtDNA deletion, known as "common deletion", causes mitochondrial dysfunction when the number of mtDNA copies with this deletion exceeds a certain threshold. Several studies have reported increased levels of mtDNA deletions in PD. Nonetheless, whether the accumulation of mtDNA deletions is somatic or depends on cell type remains unresolved. The content of circulating cell-free mtDNA (cf-mtDNA) in the cerebrospinal fluid (CSF) distinguishes idiopathic from LRRK2-related PD, suggesting that a different type of mitochondrial dysfunction underlies neurodegeneration in these two forms of the disease. We examined the presence of deletions in cf-mtDNA by simultaneously quantifying different regions of the mtDNA molecule with a novel multiplex digital PCR assay,

which allows absolute quantification of mtDNA molecules containing deletions. Using this method, we found that cf-mtDNA in CSF from patients with iPD exhibits a high proportion of deletions compared with LRRK2 mutation carriers with or without PD. Furthermore, we found that the CSF content of cf-mtDNA differentiates idiopathic from LRRK2 PD, confirming previous data. These results provide further support to the hypothesis that the mechanisms causing mtDNA dysfunction differ between idiopathic and genetic PD.

SA26. Quantification of Intrathecal Gadolinium Pharmacokinetics and Adeno Associated Virus Serotype 9 (AAV9) Biodistribution via Lumbar Puncture Versus Automated Catheter Infusion System

Gabryel Conley Natividad, Stuart Sater, Lucas Sass, Deep Singh, Omolola Bangudu, Ostin Arters, Mohammadreza Khani, Katherine Warthen, Shibi Likhite, Howard Dobson, Scott Haller, Richard Watts, Robert Switzer, Kathrin Meyer, Bryn Martin*

Introduction: Targeted delivery of genetic therapies is critical for effective treatment of CNS disorders. To bypass the blood-brain barrier and efficiently transduce terminally differentiated cells, intrathecal injections of adeno associated virus (AAV) are commonly used. The current study evaluates brain biodistribution of AAV9 through hand-administered lumbar puncture (LP) versus an automated intrathecal catheter infusion system (Catheter) via application of various assays including immunohistochemistry (IHC) staining, quantification of vector genome copies per diploid genome (VGC/DG), and dynamic contrast-enhanced MRI (DCE-MRI) with co-infusion of gadolinium (gad).
Methods: Ten seronegative female cynomolgus macaques (3-6 yrs, 4.2±1.9 kg) were co-infused with gadolinium and AAV9-CB-GFP via LP (n=5) and Catheter (n=5). The AAV9 genome was engineered to express enhanced green fluorescent protein regulated by a chicken-β-actin/cytomegalovirus hybrid promoter. Anesthesia was achieved with ketamine and maintained under isoflurane in oxygen. Calibrated DCE-MRI of gad pharmacokinetics (PK) was obtained based on pre- and post-infusion scans. Necropsy and brain harvest occurred ~21 days post-dose. Alternating 4 mm coronal brain slices were separated for IHC or biochemistry analyses. IHC slabs were fixed in paraformaldehyde and prepared for tissue slide scanning. Biochemistry slabs were punched at preselected locations, and these samples were subsequently snap frozen. IHC was ranked by visual inspection, cell count, % area stained, and VGC/DG by digital droplet PCR.

Results: Acute phase PK of gad % dose 30-min post-injection was significantly greater with Catheter vs. LP throughout the cortical gray matter (2.83±2.30% vs. 0.57±0.74%, p = 0.008, based on N=160 ROIs) and throughout the basal ganglia (0.17±0.07% vs. 0.04±0.03, p = 0.004, N=12 ROIs) (median±STD). IHC showed greater staining in the Catheter vs. LP. Similarly, average VGC/DG was +4.04X greater for Catheter compared to LP throughout the gray matter (p=0.003, N=7 tissue sample locations) and +1.27X greater in the basal ganglia (p=0.53, N=1 punch).
Conclusion: The Catheter system showed significantly higher rates of viral transduction throughout the gray matter. These findings agreed with acute phase gad PK post-injection.

SA27. 3D Computational Fluid Dynamics and In Vitro Modeling of Intrathecal Cerebrospinal Fluid Pharmacokinetics Predicts In Vivo Solute Transport of Gadolinium and AAV9 Co-infusion in Non-human Primates

*Ostin Arters, Stuart Sater, Mohammadreza Khani, Gabryel Conley Natividad, Lucas Sass, Omolola Bangudu, Richard Watts, Howard Dobson, Deep Singh, Bryn Martin**

Purpose: Preclinical testing of intrathecal pharmacokinetics (PK) plays a critical role in CNS drug research and development, yet there are no available validated tools for quantitative prediction of cerebrospinal fluid (CSF) system wide solute transport. The objective was to validate intrathecal PK model predictions with in vivo measurements in non-human primates (NHP).
Methods: Animal-specific NHP models of CSF solute transport were constructed similar to humans (1,2). CSF geometry and flow was collected in a NHP by MRI (3,4) and used to define CSF geometry and cardiac- and respiratory-induced CSF oscillations. These measurements defined the in silico 3D computational fluid dynamics (CFD) simulation and in vitro 3D printed model and utilized to simulate spatial-temporal solute PK over a 3h period following a) standard lumbar puncture (LP) with 1 mL bolus and b) injection via an automated intrathecal catheter infusion system (Catheter). Model predictions were validated by testing identical LP and Catheter protocols in N=5 NHPs per group with co-injection of AAV9 and gadolinium imaged by quantitative dynamic contrast-enhanced MRI (5). PK results were compared in terms of a) visual inspection of spatial-temporal solute transport evolution along the neuroaxis and intracranial space and b) comparison of gadolinium % of mM dose concentration in the basal cisterns.

Results: Modeling agreed with in vivo PK neuraxial distribution with the LP and Catheter groups requiring ~30-60 min and ~1-5 min to reach the foramen magnum post-injection. Quantitative comparison of gadolinium at 30 min showed % of mM dose concentration in the basal cisterns of 0.5±0.4 vs. 2.5±1.0 in vivo and 0.6 vs. 9.1 in vitro and 0.8 vs. 11.8 (%mM/mM dose) in silico for the LP and Catheter group, respectively. Visual inspection of in vivo, in silico, and in vitro solute evolution showed preferential anterior tracer movement at the basal cisterns moving caudally towards the sylvian cisterns. Little solute moved posteriorly beyond the tentorium cerebelli. No tracer was detected within the third or lateral ventricles up to 3h.
Conclusion: The in silico CFD and in vitro 3D printed model predictions were validated by in vivo CSF system-wide solute transport evolution in NHPs for specific intrathecal injection scenarios.

SA28. Anesthetic Effects and Impact of Oxytocin on Electrically Evoked Fast-Scan Cyclic Voltammetry Dopamine Signals in Dorsal Striatum of the Rat Brain

David Daberkow, Mitchell Gainer, Gracie Rosenbaum, Jair Alvarez, Darren Ginder*

Oxytocin (OXT) is involved in many aspects of brain function. Current research suggests that, due to the possible modulatory effect of OXT on learning and memory circuitry, OXT treatment for depression and addiction could be beneficial. Defining the neural mechanisms of OXT's effects on dopamine (DA) neurotransmission is critical to understanding how OXT may be therapeutic for certain psychological disorders. DA, a neurotransmitter highly implicated in learning and memory, may be modulated by OXT. In general, OXT and DA receptors are located within the same brain regions. More specifically, there is overlap in the expression of OXT and DA receptors in the dorsal and ventral striatum. Furthermore, OXT fibers innervate DA neurons. The neuroanatomical association between the dopaminergic and oxytocinergic systems provides a neurological mechanism by which OXT could potentially alter DA neurotransmission. Male Sprague-Dawley rats were anesthetized with isoflurane or urethane anesthesia. Once fully anesthetized, rats were immobilized in a stereotaxic frame, skin/fascia was cleared, and small holes drilled in the skull for placement of electrodes. A reference electrode (Ag/AgCl) was placed just below dura and a fast-scan cyclic voltammetry (FSCV) electrode was placed in the dorsal striatum (+1.0 AP, +2.0 ML, -5.0 DV). Subsequently, a stimulating electrode was placed just above the medial forebrain bundle (-4.6 AP, +1.4 ML, -7.0 DV). Constant current, biphasic stimulus pulses (60 Hz, 60 pulses, 300 µA) were applied

and the stimulating electrode was incrementally lowered until a robust DA signal was evoked. Once clear and consistent DA signals were observed, intranasal OXT (1.0 µg/kg) was administered (or an equivalent volume of saline for controls). Intranasal OXT increased DA release in the dorsal striatum, relative to controls (saline-treated rats). These results suggest OXT modulates DA neurotransmission and is potentially therapeutic for psychological disorders.

SA29. Traumatic Brain Injury Reduces Conditioned Reinforcement and Optimal Decision-Making on a Cued Rodent Gambling Task

Sarah Wampler, Jenna McCloskey, Carissa Gratzol, Garrett Sommer, Anna Gaughan, Kris Martens, Cole Vonder Haar*

Traumatic brain injury (TBI) often results in chronic deficits in decision making. These decision-making biases may be driven by impairments in discrimination of outcomes and vulnerability to cues associated with suboptimal outcomes. The purpose of this study was to determine how TBI affected conditioned reinforcement and the role of cues in decision-making and impulsivity. A TBI was delivered using the bilateral frontal controlled cortical impact injury model. At one-week post-injury, rats underwent 10 days of Pavlovian conditioning, and a conditioned reinforcement probe trial where the number of lever presses emitted to obtain the CS was recorded as a measure of incentive salience (value) of the CS. Rats were then trained on the cued rodent gambling task (cRGT) which measures probabilistic decision-making and impulsivity. During the task, rats chose between 4 options which varied in magnitude and probability of reinforcement and punishment, and magnitude of reinforcement was associated with complexity and variability of audiovisual cues. After behavior stabilized (8 weeks post-injury), rats were re-exposed to Pavlovian conditioning and tested for conditioned reinforcement. TBI decreased initial conditioned reinforcement, increased impulsivity, and decreased optimal decision making. After the cRGT, sham rats had decreased conditioned reinforcement of CS suggesting that long-term exposure to stimuli presented during reinforcement decreases conditioned reinforcement. Lesion analysis and immunohistochemistry stains of ΔFosB are in the process of being collected and will be available on the poster. These data suggest that decreased incentive salience of a CS may impair decision making in TBI population. More research is necessary to determine if increasing incentive salience will improve decision-making in TBI patients.

SA30. Analysis of Endogenous and Transplanted Stem Cell Populations Following Traumatic Brain Injury in Adult Zebrafish

Jeffery Plunkett, Andrew Pardo, Brian Avera, ismael Voltaire, Martin Oudega*

Although post-embryonic neurogenesis is limited in the mammalian brain, zebrafish (Danio rerio) retain multiple proliferative neurogenic and stem cell niches throughout adult life. The focus of our research is to study how traumatic brain injury (TBI) affects the induction of neurogenic progenitor cell fates in the adult zebrafish brain. We found that TBI induces an endogenous, quiescent population of progenitor cells that migrate from the subventricular zone (SVZ) and integrate in or near the injury zone. We hypothesize that stem progenitor populations that integrate and differentiate at or near the injury may enable the regenerative response normally seen following CNS injury in the zebrafish. Currently, we have developed a stem cell culture methodology using a rotating culture technique that develops aggregates of undifferentiated stem cells after 2-3 days. Using a proof of concept strategy, we have transplanted labeled aggregates into a TBI stab wound injury site and are currently analyzing the efficacy of integration into injury zone tissues.

SA31. Poor Glycemic Control is Associated With Worse Blood-Brain Barrier Disruption in Ischemic Stroke Patients

Richard Leigh, Andreia Faria*

Background: Elevated serum glucose is known to be associated with worse outcome after ischemic stroke. We previously identified an association between elevated glucose levels and increased disruption of the blood-brain barrier (BBB) in patients presenting with acute ischemic stroke. We sought to confirm this finding in a separate, larger cohort.
Methods: This was a retrospective analysis of a de-identified dataset of stroke patients admitted to a single comprehensive stroke center over a 10-year period. Patients were included if they had MRI performed with diffusion weighted imaging (DWI) demonstrating a stroke and perfusion weighted imaging (PWI) that showed a corresponding area of hypoperfusion. BBB disruption was measured from the PWI source images, detected as gadolinium leakage into the brain parenchyma and averaged within the perfusion deficit. Serum glucose was measured on presentation, glyco-hemaglobin (HgA1c) was measured as part of their clinical evaluation, and a history of diabetes mellitus (DM) was determined based on chart review. Results: 238 patients were included in the analysis however samples

sizes varied based on available data. The median age was 61 and 45% were women. More severe BBB disruption was associated with larger stroke volume ($p<0.001$, n=238), higher NIHSS ($p<0.001$, n=163), and higher serum glucose ($p=0.044$, n=185) but not age ($p=0.495$, n=238), sex ($p=0.466$, n=238) or history of DM ($p=0.660$, n=238). Higher HgA1c level showed a trend for worse BBB disruption ($p=0.095$, n=186) and was included in the multivariate analysis. Elevated serum glucose remained associated with increased BBB disruption ($p=0.012$, n=155) when controlling for stroke volume ($p<0.001$) and NIHSS ($p=0.209$). Higher HgA1c was associated with more severe BBB disruption ($p=0.008$, n=158) when controlling for stroke volume ($p<0.001$) and NIHSS ($p=0.042$). Serum glucose and HgA1c were not independent of each other when added to the same model.
Conclusions: Poor glycemic control at the time of, and leading up to, an ischemic stroke is associated with more severe BBB disruption within the ischemic lesion independent of stroke lesion size or clinical severity. BBB disruption may represent a marker, or potentially a target, for treatments aimed at diminishing the negative impact of hyperglycemia on stroke outcomes.

SA32. Novel, Thalidomide-Like, Non-Cereblon Binding Drug Tetrafluorobornylphthalimide Mitigates Inflammation and Brain Injury

*Daniela Lecca, Shih-Chang Hsueh, Weiming Luo, David Tweedie, Dong Seok Kim, Abdul Mannan Baig, Neil Vargesson, Yung-Hsiao Chiang, Barry Hoffer, Nigel Greig**

Tetrafluorobornylphthalimide (TFBP) and tetrafluoronorbornylphthalimide (TFNBP) were generated to retain the core phthalimide structure of the immunomodulatory imide drug (IMiD) class that is linked to a bridged ring structure to retain the beneficial anti-inflammatory properties but, importantly, hinder cereblon binding that underlies the adverse action of classical thalidomide-like IMiDs. TFBP and TFNBP reduced markers of inflammation in mouse macrophage-like RAW cell cultures and in rodents challenged with lipopolysaccharide, lowering proinflammatory cytokines. Binding studies demonstrated minimal TFBP or TFNBP interaction with Cereblon, with no resulting degradation of teratogenicity-associated transcription factor SALL4. To evaluate the biological relevance of its anti-inflammatory actions, TFBP was administered to mice following controlled cortical impact (CCI), moderate severity, traumatic brain injury (TBI). Compared to vehicle treatment, TFBP reduced TBI lesion size together with activated microglial cell number, as evaluated by immunohistochemistry 2-

weeks post injury. Behavioral evaluations at 1- and 2-weeks post injury demonstrated TFBP provided more rapid recovery of TBI-induced motor coordination and balance impairments, versus vehicle treated mice. TFBP and TFNBP represent a new class of IMiDs that lower proinflammatory cytokine generation but lack binding to cereblon (associated with the teratogenicity of classic thalidomide-like drugs) and provide a strategy to mitigate excessive neuroinflammation associated with moderate severity TBI to, thereby, improve behavioral outcome measures.

SA33. Leveraging Mouse and Rat Brain Atlases to Standardize Brain-Wide Mapping in Serial Sections and Cleared Intact Brain Volumes Across Experiments

*Nathan J. O'Connor, Aidan E. Sullivan, Brian S. Eastwood, Paul J. Angstman, Arthur D. LeDuc, Nathan D. Liese, Charles R. Gerfen, Jacob R. Glaser, Shane Baldwin**

Molecular neuroanatomical methods have significantly improved the ability to identify and map the connections of neuron subtypes and circuits in behavioral and pathologic models. Analysis of connectivity in mouse and rat brains that are subsequently registered to standardized digital reference atlases reveals new details about the functional organization of brain circuits related to behavior and pathologies and enables comparison of data across animals, experiments, and laboratories. We present the results of applying a comprehensive workflow for cell detection within images of histologically-processed mouse and rat brains, followed by mapping to the Allen Mouse Brain Atlas and the Waxholm Rat Brain Atlas respectively. The cell detection algorithms we used employs neural networks that were trained with an iterative active learning process involving manual auditing of detected cells in randomly selected regions of interest across many training images. We have employed this active learning approach to build neural networks that are tailored to detection of specific cell types. Following cell detection, we employ novel registration methods to align multiple serial section images to the atlas spaces. Through validation studies, we have shown that our registration algorithms account for non-orthogonal sectioning and tissue deformities introduced during histological processing. Registration enables mapping the populations of detected cells into the atlas' common coordinate framework. Correlations and comparisons among cell populations from different individual animals are subsequently performed in the atlas space. We also present results of successfully employing workflows for cell detection and registration methods to cleared brain tissue imaged by light sheet microscopy, incorporating cell population analysis on 3D

images of mouse and rat brains registered to the corresponding atlas space. Together, these workflows provide a unified approach to analysis of both histologically sectioned brain tissue and intact cleared brain tissue from multiple individual animals, experiments, and laboratories.

SA34. Chronic Administration of JWH-133 (Cannabinoid Receptor 2 Agonist) Increases Ectopic Ovarian Tumor Growth and Endocannabinoids Levels in Immunocompromised SCID Female Mice

Melissa McHann, Isabel Castro-Piedras, Josee Guindon*

Cannabinoid-based therapies are increasingly being used by cancer patients to treat chemotherapy-induced nausea and vomiting. Recently, cannabinoids have gained increased attention for their effects on cancer growth. Indeed, the effect of CB2 (JWH-015, JWH-133) agonists on breast cancer models have shown to reduce the size of breast cancer tumors. However, these studies assessing breast cancer progression were using CB2 agonist administered early into the cancer progression therefore assessing their effects on already established tumors is a critical need. In our study, we evaluate tumor growth using an ectopic xenograft ovarian (SKOV-3 and OVCAR-5) cancer model. The impact of chronic (30 days) administration of CB2 (JWH-133) agonist will be evaluated and started on 30 days of ectopic ovarian tumors. We will then evaluate and determine the mechanisms involved in ovarian cancer tumor growth by measuring levels of anandamide and 2-arachidonoyl glycerol as well as protein levels of CB1, CB2, ERα, ERβ, GPER, TNFα, IL-1β and IL-6 in ovarian and tumor tissues. Our results demonstrate a significant increase in ectopic ovarian tumor growth following chronic administration of JWH-133, but not after administration of ACEA. Ovarian cancer tumor tissues chronically (30 days) treated with JWH-133 in comparison to vehicle treated groups showed an increase in endocannabinoid (AEA and 2-AG) and protein (CB2 and TNFα) levels with a decrease in GPER protein levels. Interestingly, our study emphasizes the importance of studying the impact of cannabinoid compounds on already established tumors to improve our understanding of cannabinoid-based therapies and, therefore better address clinical needs in cancer patients.

SA35. A Dopaminergic System Promoting Sniffing

Natalie Johnson, Anamaria Cotelo, Andy Chavez, Minghong Ma, Daniel Wesson*

Sniffing is a widely observed behavior reflecting motivational states. For example, rodents sniff during social interactions, while foraging for food, and even in anticipation of a reinforcer in instrumental tasks. The brain systems mediating this conserved and adaptive behavior are unknown. Here we sought to link displays of sniffing with the dopaminergic (DAergic) system. We hypothesized that DA release in the tubular striatum (TuS, also known as the olfactory tubercle), a component of the ventral striatum receiving both midbrain DAergic input and olfactory sensory input, is integral to sniffing behavior. In mice of both sexes, we first established that the TuS, especially the anteromedial portion, is recipient of dense input from ventral tegmental area (VTA) DAergic neurons, and through transsynaptic tracing, that VTA neurons synapse onto TuS neurons. To validate that VTA TuS DAergic input is behaviorally relevant, we used an optical intracranial self-stimulation task and found that this input is reinforcing and supports approach behaviors. Next, using in vivo fiber photometry and whole-body plethysmography, we observed that phasic DA release in the TuS is tightly coupled to the display of individual sniff bouts, including both spontaneous and sensory-evoked bouts. Further, causal manipulations revealed that while optical stimulation of DA release in the TuS triggers sniff bouts, pharmacological inhibition of DA1 and DA2, but not DA3 receptors, in the TuS reduced both the number and vigor of sniff bouts. Similar-sized effects were not observed in the nucleus accumbens. Together these results implicate DAergic actions within the TuS in the orchestration of sniffing and uncover a system supporting this widely displayed motivated behavior.

SA36. Chronic Morphine Has Opposing Effects on Opioid Signaling Within a Thalamo-Cortico-Striatal Microcircuit

Elizabeth Jaeckel, Erwin Arias-Hervert, Alberto Perez-Medina, Kyle Ramsey, William Birdsong*

Opioid effects are mediated through activity at the mu-opioid receptor (MOR). Prolonged opioid use results in tolerance to their pain-relieving properties but sensitization to other properties, such as reward and locomotor stimulation. The differential cellular adaptations underlying these opposing phenomena are not well understood, but one possibility is that effects of chronic opioid exposure vary based on receptor location.

MORs are present both at cell bodies (somatic) and within axon terminals (presynaptic). Chronic opioid exposure typically results in cellular tolerance at cell bodies of MOR-expressing neurons, but little work has been done studying chronic opioid effects on synaptic transmission within axon terminals. Medial thalamic projection neurons send glutamatergic afferents to the striatum and anterior cingulate cortex (ACC) and express both somatic and presynaptic MORs. Here, we determined the effects of chronic morphine exposure on morphine signaling at thalamo-striatal terminals, thalamo-cortical terminals, and cell bodies of thalamic neurons. These brain regions are important sites of opioid action, providing a relevant circuit in which to study chronic opioid effects within the same neuronal population. We used patch clamp electrophysiology and optogenetics to measure opioid signaling at presynaptic and somatic receptors in brain slices of drug-naive and morphine treated mice. Chronic morphine caused tolerance to morphine signaling at thalamo-cortical terminals but facilitation of morphine signaling at thalamo-striatal terminals. These effects were only observed in brain slices from male mice. At medial thalamic cell bodies, chronic morphine treatment did not affect morphine signaling. The finding that chronic morphine induced opposing adaptations within the same population of neurons suggests a role of several factors, such as cell type, brain region, and receptor subcellular location in determining chronic opioid effects at the cellular level.

SA37. The Influence of Mood State on Self-Assessment in Patients With Schizophrenia and Bipolar Disorder

Felicia Gould, Philip Harvey, Michele Perez, Bianca Tocero, Jean Marie Henry*

Self-assessment deficits are well established across all populations, including the healthy controls. Sad moods have been found to be related to attenuated misestimation of performance, but depression has been reported to lead to underestimation of everyday functional capabilities. Momentary self-assessment of cognitive performance, as well as self-reports of overall cognitive ability and every day functioning were examined in participants with schizophrenia (N=124) and bipolar disorder (N=113), with momentary assessments of negative affect (NA) collected with ecological momentary assessment (EMA). In schizophrenia, momentary self-assessments of functioning were not correlated with cognitive performance and were not predicted by momentary NA. In bipolar disorder, cognitive performance and momentary self-assessments

were correlated, but misestimation of performance was significantly predicted by clinical ratings of depression (p >.01) and greater NA (p >.01). In both patient groups all correlations with self-reported global functioning and increased depression and more negative affect were negative and statistically significant. Sad moods were associated with momentary challenges in self-assessment only in bipolar disorder, while in both groups greater sadness and depression are correlated with self-reports of poorer global functioning.

SA38. Bacteroides Spp. HB-32 Rescues Behavioral Phenotypes in Sleep Deprivation- and Social Defeat Stress-Induced Models of Depression

*Stephen Skolnick**

A growing body of work implicates the gut microbiome in the etiology of depression, schizophrenia, and other neuropsychiatric diseases, but the ecosystem's depth and complexity have made it difficult to identify actionable solutions based on the existing data. Here, we report the efficacy of a human gut-derived Bacteroides strain, HB-32, in reversing behavioral phenotypes associated with depression in two rat models. In a social defeat stress-induced model, HB-32 rescued sucrose preference comparable to ketamine. In a sleep deprivation-induced model, time spent immobile in a tail-suspension test was reduced to levels comparable to no-sleep-deprivation controls.

Sunday, January 22, 2023

POSTER SESSION II
3:30 PM - 4:30 PM
BALLROOMS 2 & 3

SU1. The Role of the Lateral Habenula in Individual Susceptibility to Opioid Abuse

Christopher O'Brien, Dhruvi Desai, Roshni Vemireddy, David Barker*

Opioids are widely prescribed and highly effective for treating acute pain. Although opioids have high abuse liability, only a subset of individuals transition to abuse while others remain resilient. Predicting specific individual susceptibility to opioid use disorder (OUD) is limited, in part because OUD is often comorbid with other psychological illnesses such as depression or anxiety. One known risk factor for OUD as well as for depression or anxiety is a history of stressful or traumatic experiences. Thus, stress may act to trigger individual differences that help determine the risk for developing a substance use disorder and for future drug relapse. We recently discovered that mice with a history of stress exhibit a specific profile of negative valence and pain-related behaviors that can predict opioid abuse susceptibility. Specifically, we discovered that heightened mechanical sensitivity to pain following stress, in combination with heightened sucrose preference predicts individuals with a stronger propensity for fentanyl seeking. Conversely, we observed that control mice who show low sucrose consumption, often thought to be a sign of anhedonia, also exhibit the greatest risk for fentanyl seeking. When taken together, these data suggest that stress acts as a trigger for broad changes in the behavioral profile associated with OUD risk. In trying to determine the neural substrate supporting these changes, we first turned to the lateral habenula (LHb). The lateral habenula (LHb) is important for processing aversive stimuli, modulating responses to reward, and has known roles in pain and depression. Here we have modulated the activation of the habenula using inhibitory hM4D(Gi)-DREADDS during our shock paradigm. Our results show that this inhibition of the LHb can block the induction of mechanical hypersensitivity following stress.

SU2. Inhalation Self-Administration of Heroin and Nicotine in Middle Aged Rats

Michael Taffe, Arnold Gutierrez*

Recent US lethality statistics show increasing deaths due to opioids over the past two decades, including a steep increase in heroin-related deaths from 2011, and from synthetics such as fentanyl from 2014, onward. An unexpectedly steep rise in the drug-related overdose rate for middle aged to older adults (50-65) in recent years has placed attention on the specific health risks for this population. Lethality data are but the tip of the iceberg of the total problem of opioid use disorders and the behavioral and physiological impact of age on opioid effects, toxicity and addiction in middle aged rats is almost entirely unexplored in the scientific literature. These studies use vapor inhalation as the route of self-administration to better match human routes and as a practical improvement for longitudinal studies in rats across ~half of their lifespan. The anti-nociceptive effects of heroin (0.5-1.56 mg/kg, s.c.) do not differ from adolescence to young adult and middle-aged adulthood in rats. Female rats self-administer more heroin vapor (50 mg/mL in PG vehicle) than do male rats, across adult ages, however middle-aged rats self-administer similarly to young adult rats. The studies also show that repeated intensive exposure to nicotine vapor in adolescence does not alter the vapor self-administration of nicotine or heroin in middle age. Finally, the direct volatilization of heroin HCl reinforces drug seeking behavior similar to the delivery of heroin vapor from an e-cigarette type device.

SU3. The Impact of EcoHIV Infection on Cocaine-Related Behaviors

Qiaowei Xie, Joshua Jackson, Jacqueline Barker*

Substance use disorders (SUDs) are characterized by high propensity to relapse and are highly comorbid with HIV infection. The neurobiology underlying this relationship is poorly understood. Preclinical research on the neurobiobehavioral outcomes of progressive HIV infections may yield crucial information to improve SUD prognosis and reduce relapse in people living with HIV (PLWH). To model progressive HIV, adult male and female C57BL6J mice were inoculated with EcoHIV, a chimeric HIV-1 which infects rodents, or with vehicle as sham control. We investigated the cocaine-induced locomotor sensitization in EcoHIV infected mice by

assessing locomotor activity after repeated cocaine exposure (10mg/kg). We found that EcoHIV infected mice sensitized locomotor more rapidly than shams. In a separate cohort of mice, cocaine reward learning and seeking were assessed using conditioned place preference (CPP) paradigm. Cocaine- and yohimbine-induced reinstatement were assessed following extinction training. EcoHIV mice showed significantly reinstatement in both tests compared to sham control mice. Finally, we assessed whether neuronal activation by cocaine is altered by EcoHIV infection. Putative cocaine-induced activation in the prefrontal cortex (PFC) and nucleus accumbens (NAc) was assessed in brains collected 90 minutes after cocaine exposure through quantitative analysis of expression of the immediate early gene, cFos. We found that cocaine interacted with EcoHIV infection to increase neuronal activation selectively within the infralimbic PFC and NAc shell subregions. These findings suggest that progressive EcoHIV infection may involve neurobiological plasticity within accumbal circuits that promotes behavioral changes and may have implications for factors precipitating risk for drug relapse in PLWH.

SU4. Measuring the Effect of Neuropathic Pain on Drug-Seeking Ensembles in the DMPFC

Bailey Sarka, Shuai Liu, Qing-Song Liu, Cheryl Stucky, Chris Olsen*

Approximately 50 million Americans suffer from chronic pain, and opioids are commonly prescribed for such individuals. Unfortunately, nearly a quarter of chronic pain patients have reported misusing their prescription. We are investigating the effect of chronic pain on drug-seeking behavior at the neuronal level. Repeated drug-seeking is associated with reactivation of an ensemble of neurons sparsely scattered throughout the dorsomedial prefrontal cortex (dmPFC). Prior research has demonstrated that chronic pain increases intrinsic excitability of dmPFC neurons, which may increase the likelihood of reactivation during drug seeking. We tested the hypothesis that chronic pain would increase oxycodone seeking behavior, and that the pain state would differentially increase intrinsic excitability in dmPFC drug seeking ensemble neurons. TetTag mice self-administered intravenous oxycodone. After 7 days forced abstinence, a drug seeking session (extinction conditions) was performed and the ensemble was tagged. Mice received spared nerve injury (SNI) to induce chronic pain during the period between a first and second seeking session, and we measured persistence of seeking between the two

sessions to determine if the SNI exacerbates seeking. Following the second seeking session we performed electrophysiology on individual neurons within the dmPFC to assess intrinsic excitability of the drug-seeking ensemble and non-ensemble neurons. We found significant sex differences in the effect of SNI on oxycodone seeking and electrophysiology, such that the induction of chronic pain can modulate seeking behavior in mice that have previously self-administered oxycodone prior to injury.

SU5. The Ventral Tegmental Area Has Glutamatergic Neurons That Play a Role in Cocaine Seeking-Behavior

Flavia Barbano, Jia Qi, Emma Chen, Marisela Morales*

Converging evidence indicates that dopamine and glutamate neurotransmission within the nucleus accumbens (NAc) play a role in drug addiction. Increases of NAc dopamine release from ventral tegmental area (VTA) inputs encode the rewarding effects of drugs of abuse. In contrast, NAc glutamate release from prefrontal cortex inputs synapsing on NAc medium spiny neurons play a role in cocaine reinstatement. We have demonstrated that, in addition to dopamine neurons, the VTA has glutamate neurons that also target the NAc and establish excitatory synapses on parvalbumin GABAergic interneurons. Here, we determined whether this glutamatergic pathway from VTA to NAc-parvalbumin interneurons plays a role in cocaine-seeking behavior. By expressing Channelrhodopsin in mouse VTA glutamatergic neurons, and by NAc photostimulation, we evoked local release of glutamate from VTA glutamatergic axons. By conditioned place preference (CPP) task, we evaluated the role of NAc glutamate release (evoked by local photostimulation of VTA glutamatergic inputs) during the acquisition, expression or reinstatement of cocaine-induced CPP. We found that NAc photostimulation of VTA glutamatergic inputs did not alter CPP acquisition, but inhibited both CPP expression and reinstatement behaviors. In another set of mice expressing Channelrhodopsin in parvalbumin interneurons, we found that direct photostimulation of the whole population of NAc parvalbumin neurons did not modify CPP acquisition, expression, or the reinstatement. From these findings, we concluded that: VTA neighboring dopamine and glutamate neurons innervating the NAc play different roles in cocaine reward; NAc glutamatergic inputs depending on their source (cortex or VTA) and specific neuronal targets (medium spiny neurons or parvalbumin

interneurons) differentially modulate cocaine-seeking behavior; a selective population of NAc parvalbumin neurons, regulated by VTA glutamatergic neurons, play a role in cocaine-seeking behavior.

This study was supported by the Intramural Research Program of the National Institute on Drug Abuse

SU6. Chemesthetic Perception Gates Orosensory Acceptance of Alcohol

Snigdha Mukerjee, Keaton Song, David Cohen, Vikrant Mahajan, Alex Brown, Cody Siciliano*

Ethanol is highly unusual among acutely toxic chemicals in that it will be repeatedly consumed by essentially all animal species when given access. The central pharmacological effect of ethanol mediates its powerful reinforcing properties but the neural mechanisms that control palatability of ethanol and explain individual differences in innate preferences prior to intoxication are unknown. When ethanol is not available, heavy drinkers often consume poisonous ethanol-containing solutions, such as gasoline and mouthwash, suggesting that chronic ethanol use disrupts innate chemical defense systems responsible for oral rejection of toxins. Ethanol has a complex flavor profile, evoking a range of gustatory or taste sensations in addition to a burning-tingling sensation (termed oral chemesthesis) which becomes dominant at high concentrations. Oral chemesthesis is distinct from traditional taste qualities and is detected by the trigeminal innervation. Here we reveal the circuits that sense concentrations of chemical irritants in the mouth and directly report to the brainstem, to determine whether ethanol is consumed or rejected. Neural coding of oral chemesthesis is under-studied, we first identified the structural and functional brain regions that respond to 50% ethanol, a relatively high concentration known to elicit strong chemesthesis. These results revealed that the trigeminal ganglion is centrally positioned for relaying chemical information from the mouth. Using pharmacological and chemogenetic interventions combined with in vivo imaging we identified peripheral to central circuits and cellular targets that influences palatability of ethanol thereby altering motivation and consumption. Altogether, the present findings elucidate how ethanol bypasses the gating mechanism in the mouth to allow ingestion of a substance with a dominant burning-tingling irritant like flavor. Further, the cellular targets uncovered in these studies illuminate novel drivers of substance use behaviors and may provide a mechanism for hypofunction of this system within chronic ethanol users.

SU7. Enhanced Excitability and Excitatory Transmission in Noradrenergic NTS Neurons Following Precipitated Morphine Withdrawal

Anthony Downs, Zoe McElligott*

Repeated bouts of opioid consumption and withdrawal induce long-term changes in stress and reward circuitry in the brain that promotes further opioid consumption and opioid use disorder. The noradrenergic A2 cell group located in the nucleus of the solitary tract is an important mediator of stress responses and is activated during morphine consumption and withdrawal. Understanding the neurobiology of withdrawal, and how withdrawal contributes to the development of opioid use disorder (OUD), is critical for the development of new treatments for OUD. Here, we administered morphine and then precipitated withdrawal using naloxone, administered morphine and subsequent saline (spontaneous withdrawal), or saline and naloxone (naloxone control) over 3 days to investigate behavioral and cellular responses on day 4 to withdrawal using patch-clamp electrophysiology. Mice undergoing precipitated withdrawal exhibit behavioral sensitization to withdrawal behaviors across the 3-day paradigm. We found changes in spontaneous EPSCs in the A2 neurons of precipitated withdrawal mice that are consistent with increased calcium-permeable AMPA receptors, and these effects are reversed by the calcium-permeable AMPA receptor antagonist NASPM. We further found increased baseline firing frequency of A2 neurons, decreased afterhyperpolarization potential, and increased AP halfwidth following precipitated withdrawal as compared to the morphine or naloxone alone groups. Finally, we found increased A2 neuron excitability in precipitated withdrawal animals. Together these data demonstrate significant changes in excitatory transmission and excitability in A2 neurons that could underlie the behavioral effects of morphine withdrawal. Future studies are needed to address the functional significance of these physiological changes.

SU8. Can Porn Be Addictive? Results of Comparative VBM, DTI and fMRI Studies and Randomized Clinical Trial

Mateusz Gola, Małgorzata Draps, Michał Lew-Starowicz, Guillaume Sescousse, Ewelina Kowalewska, Natalia Kowalczyk, Katarzyna Obarska, Marc Potenza*

In 2022 WHO included Compulsive Sexual Behavior Disorder (CSBD) in the 11th edition of the International Classification of Disorders. Majority of people meeting CSBD criteria seek treatment for problematic pornography use (PPU). There is a lack of consensus, how to conceptualize PPU. Therefore, in the series of 3 studies we have examined structural (VBM, DTI) and functional (fMRI) brain similarities and differences between 82 individuals with PPU, 28 with Alcohol Use Disorder (AUD), 22 with Gambling Disorder (GD), Obsessive Compulsive Disorder (OCD) and 76 healthy control (HC) subjects. In the 4th study, we have assessed brain activity (fMRI) before and after 5-month pharmacological treatment (randomized clinical trial with paroxetine, naltrexone and placebo) in a group of additional 72 individuals with PPU. Results uncovered similarities between PPU, AUD and GD in lower prefrontal cortex (PC) volume (VBM) when compared to HC and showed negative relation between anterior cingulate cortex (ACC) volume and severity of symptoms. Results of DTI are not conclusive and suggest that PPU shares similarities both with OCD and AUD. Results of fMRI assessed during the incentive delay task with monetary and erotic trials uncovered increased cue-reactivity (specific for erotic but not monetary cues) in ventral striatum (VS) and orbitofrontal cortex (OFC) among PPU subjects and suggest incentive sensitization in this group. VS sensitization was positively related to clinical symptoms. Results of our randomized clinical trial show that both active arms of treatment (compared to placebo) resulted in decreased VS sensitization and symptoms improvement after the treatment.

Our results suggest that PPU may share similar structural vulnerabilities (e.g. decreased VBM in PC and ACC) to AUD and GD, and is related to incentive sensitization for erotic cues. Functional alteration in VS and OFC may play a causal role in PPU and can be partially reversed with pharmacological treatment.

SU9. Compartment-Specific Mesolimbic Dopamine Dynamics in Contingency Learning

Suzanne Nolan, Kirsty Erickson, Patrick Melugin, Michelle Kwon, Hannah Chen, Alex Brown, Hannah Branthwaite, Erin Calipari, Cody Siciliano*

Despite the prevalence and global financial burden of substance use disorders (SUDs), the pathophysiology is poorly understood, and current treatments have limited efficacy. However, deficits in reward learning and motivation characteristic of SUDs can be directly linked to experience-induced alterations in dopamine transmission in the ventral tegmental area (VTA) to nucleus accumbens (NAc) pathway, mainly via ex vivo measurements of dopamine release in the nucleus accumbens terminals. Conversely, little is known about the roles of non-canonical forms of release such as somatodendritic dopamine (sDA) release within the VTA, due to technical limitations which have largely prevented high fidelity temporally-specific recording of sDA signatures. Here, we utilized multisite fiber photometry and the optical sensor dopamine dLight1.2 to record in vivo somatodendritic dopamine kinetics at baseline as well as during a complex discriminative learning operant task and compare these to terminal release signatures. Our results revealed distinct activity-dependent signatures across contingency learning in the two compartments, characterizing these rapid time-locked sDA release signatures for the first time. Next, we examined several potential mechanisms for this compartment-specific plasticity using widefield imaging of dLight dynamics and fast-scan cyclic voltammetry in ex vivo slices containing either the accumbal dopamine terminals or ventral tegmental area dopamine somata. Our results indicate enhanced high-frequency evoked dopamine release in the NAc terminals following contingency learning compared to naïve controls. However, in the VTA, the peak of evoked sDA release was unchanged in animals that underwent learning procedures. Together, these data suggest that sDA release is functionally decoupled from axonal release during motivated behavior and supports our growing hypothesis that sDA release is activated by appetitive stimuli only after complex reinforcement learning has occurred. Further, the results of these experiments support temporally- and compartment-specific roles of dopaminergic plasticity in basal cognitive functions like reinforcement and motivated learning, and ultimately further extend our understanding of dopamine's role in both health and disease.

SU10. Predicting Relapse With the Entire Animal's History of Cocaine-Evoked Dopamine Responses

Miguel Lujan, Natalie Zlebnik, Reana Young-Morrison, Sheila Engi, Brandon Oliver, Lanyuan Zhang, Joseph Cheer*

Increased vulnerability to relapse results from maladaptive potentiation of the mesolimbic dopamine (DA) system. However, technical limitations have so far precluded the formulation of an unambiguous "dopaminergic hypothesis" of relapse that does not introduce artificial manipulations that alter the DA substrate (e.g., optogenetics, chemogenetics, lesions, etc.). Other determinants of relapse to cocaine use, such as sex, also remain insufficiently explored. Here, we utilize GrabDA-based fiber photometry to uncover cocaine-evoked, phasic DA responses in the NAc, from acquisition to reinstatement of cocaine self-administration. Our results indicate that relapse behavior was robustly correlated with the amplitude of cocaine-evoked NAc DA transients observed on earlyacquisition and progressive ratio sessions. Using a principal component regression approach, we showed that multivariate patterns of NAc DA release, comprising the whole history of each animal's DA responses, explained cue-induced reinstatement behavior to a high degree of accuracy (R2 = 0.73). In our dataset, males displayed increased DA fluorescence on virtually every phase of voluntary seeking and intake of cocaine. Notably, the combination of sex and the patterned DA release yielded a remarkably accurate prediction of the reinstatement, reproducing 82% (R2 = 0.82) of the observed variance. We also observed a greater resistance to cease voluntary cocaine-seeking during extinction responding in males. Using a Cox proportional hazards model, patterned DA responses and sex were used to predict the transition to cocaine-seeking extinction. The Cox model accurately fit the observed extinction survival curves and recapitulated the slower extinction rates displayed by males. In conclusion, our experiments show that it is possible to recapitulate reinstatement and extinction with a simple linear model that integrates the animal's longitudinal repertoire of cocaine-evoked phasic DA responses in the NAc and its sex. Fiber photometry in self-administering mice allowed us, for the first time, to characterize sex-specific phasic dopamine responses during the voluntary pursuit of cocaine.

SU11. CRISPR-Based Manipulation of Kv7 (KCNQ) Channel Subunits Reveals Unique Contributions to Striatal Neuron Activity

Emily Jorgensen, Alexa Tellez, Jeremy J. Day*

KCNQ “m-type” K+ currents are important for controlling neuronal excitability, serving as a brake against hyperexcitable states in neurons. As such, changes in KCNQ channel expression and activity have been implicated in several neuropsychiatric disorders including substance abuse. KCNQ channels in the nucleus accumbens are altered by cocaine exposure and are required for cocaine conditioned place preference. While KCNQ subunits are encoded by a family of genes (Kcnq1 - Kcnq5) that form tetrameric channels, most prior work has used pharmacological approaches that lack genetic specificity. Additionally, little is known about subunit-specific contributions to reward circuitry and drug-seeking behaviors. To better understand the function of KCNQ channels in the striatum, we engineered CRISPR sgRNAs targeting the promoters for rat KCNQ subunit genes Kcnq2 and Kcnq3 to permit subunit-specific CRISPR activation/interference strategies. Our results demonstrate robust and bidirectional regulation of Kcnq2 and Kcnq3 in rat primary striatal neuron cultures, with potential cross-talk between Kcnq2 and Kcnq3 expression levels. To measure the role of KCNQ subunits on electrophysiological activity, we paired CRISPR manipulations with high-density multielectrode array recordings from striatal neurons. Notably, Kcnq3 knockdown selectively increased action potential frequency, while overexpression of either Kcnq2 or Kcnq3 decreased spontaneous activity compared to non-targeting lacZ controls. These results supplement our previous findings of differential responses to pharmacological manipulation of KCNQ2/3 channels in the same cells, further demonstrating an important role for KCNQ channels in striatal cell function. Future studies will expand these results to determine how genetic manipulation of Kcnq2 and Kcnq3 affects striatal neuron responses to dopamine. These experiments will continue to provide insight into the physiological changes involved in substance use disorders.

SU12. Emerging Activity Dynamics and Noradrenergic Modulation of Prelimbic Cortical Neuronal Ensembles During Heroin Seeking

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Cue-induced drug seeking requires activation of the prelimbic prefrontal cortex (PL) that is dysregulated in substance use disorder. The heterogeneity in PL cell types has made it difficult to unveil the precise PL circuit dynamics which orchestrate drug seeking. To address this, we developed a head-fixed heroin self-administration procedure to allow longitudinal tracking of PL neuronal activity during behavior. To measure the activity of PL projection neurons, we virally labeled these neurons for calcium imaging (AAVdj-CaMKIIa-GCaMP6s) and implanted a GRIN lens dorsal to PL. Subsequent two-photon recordings reveal both frequency and amplitude of calcium events in PL neurons are reduced following acquisition of heroin seeking, effects which persist through extinction, but then resurge during reinstatement (RST) in a manner time-locked to cue presentation. As local noradrenergic signaling rapidly increases PL activity and mediates drug-cue memory retrieval, we hypothesized that inputs from the locus coeruleus (LC) contribute to rescue of PL activity during RST. We found that chemogenetic inhibition of LC-PL axon terminals blocks cue-induced RST, an effect which surprisingly persisted upon a subsequent cue test. These effects were specific to drug cues, as LC-PL inhibition neither persistently suppressed stress- or drug-primed heroin-seeking RST nor affected cued-induced sucrose-seeking RST. Interestingly, we found suppressed cue-induced RST coincides with suppressed excitatory activity in a discrete PL cell cluster which ordinarily decodes the drug-cue. Preliminary studies suggest effects are due to disruption of retrieval, rather than reconsolidation, of drug-cue memories. Ongoing analyses aim to assess sex differences and changes in single-cell activity dynamics throughout heroin self-administration, extinction, and RST. These studies suggest LC-PL axon activation rescues excitatory activity in downstream PL projection neurons for cue-induced RST of heroin seeking.

SU13. Amygdalar-Cortical Circuit Determinants of Social Isolation-Associated Alcohol Consumption

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Although there are correlations between social isolation and increased alcohol consumption, as further supported by the surge in alcohol sales and use during the COVID-19 pandemic, little is known about the neurobiological mechanisms underlying these phenomena. What brain changes are induced by social that trigger alcohol drinking? To address this question, we used a combination of behavior, ex vivo patch electrophysiology, optogenetics, cellular resolution calcium imaging, and machine learning. We found that social rank predicts alcohol drinking, where subordinates drink more than dominants, and that social isolation further increases alcohol drinking in all mice, while decreasing sucrose drinking. We then found that social isolation increases neural excitability in the basolateral amygdala (BLA), and stimulating BLA terminals in the medial prefrontal cortex (mPFC) is sufficient to increase consumption of alcohol. To reveal how social isolation modifies BLA representations of alcohol, we used longitudinal cellular-resolution calcium imaging and machine learning. We found that alcohol responsive amygdala functional clusters turnover following social isolation. To determine the impact of amygdala functional turnover on representation of alcohol, we used a generalized linear model (GLM) and found population-level amygdala dynamics was sufficient to decode alcohol verses water consumption, and social isolation increases GLM decoding performance. In contrast, social isolation decreases GLM decoding performance of sucrose verses water consumption, consistent with the diametrically opposing effects of social isolation on alcohol and sucrose consumption. To then determine how amygdala inputs can modify mPFC representations of alcohol, we combined optogenetics and imaging and found that amygdala-cortical terminal activation abolishes positive valence responses to sucrose without altering negative valence responses to shock, suggesting that the amygdala-cortical circuit induces a negative affective or loneliness-like state by inhibiting positive encoding cortical neurons which may motivate alcohol use. Together, we identified a cellular substrate of social isolation and resolved a role for the amygdala-cortical circuit in social isolation-induced escalated alcohol drinking.

SU14. *POSTER WITHDRAWN*

Characterizing the Novel Mechanisms Underlying Serotonin Dependent Regulation of Behavior

Gareth Harris, Delyar Khosroabadi, Skylar Labrie, Jamie Ferns, Krysta Korpontinos, Lendin Stell Santiago*

Brain targeting drugs and their actions have been an intensive area of

research as potential therapeutics for neurological disorders. Despite the use of an array of pharmacological therapeutics for targeting neurological mechanisms associated with depression, understanding of the mechanisms underlying these processes and the exact targets of each pharmacological drug is still not fully understood. More recently, there has been a deeper focus on understanding novel mechanisms that mediate modulatory effects from key biogenic amines, including serotonin, neuropeptides and electrical junctions in mood, emotion and reward. These neural molecules have also been implicated in a variety of diseases, such as, Major Depressive Disorder, Bipolar Disorder, anxiety and addiction. We are currently investigating the effects of Serotonin on intracellular pathways and sensori-motor networks. We use Caenorhabditis elegans, to investigate the effects of serotonin on key worm behaviors. We are currently examining genetic mutants that lack gene families encoding neurotransmitters, neuropeptides, intracellular signaling and electrical junctions for any role in serotonin effects on worm egg laying and movement. With many of the C. elegans genes sharing significant conservation with humans, this provides a potential avenue to identify effects of human targeting compounds that are still not fully understood. We have begun to characterize the role of novel intracellular neuronal signals and synaptic and non-synaptic information flow that is required for serotonin-dependent stimulation of egg laying and inhibition of movement(paralysis). Specifically, we have, 1) Identified multiple neural signaling molecules that mediate the serotonin-dependent effects, including, 2) synaptic transmission genes, select neurotransmitter genes, neurosecretory signal encoding genes, and, 3) identified heterotrimeric G-protein signaling mechanism's that are required or interact with serotonin- dependent effects on egg laying and movement. We propose using C. elegans as a platform for continued study of serotonin-dependent effects on sensory, motor, and muscle dependent behavioral output.

SU15. Lesion Symptom Mapping of Appetite

*Emily Dappen, Joel Bruss, Brandon Neisewander, Daniel Tranel, Aaron Boes, Nick Trapp**

Background: Alterations of appetite are associated with numerous neuropsychiatric and medical conditions including depression, anxiety, anorexia nervosa, frontotemporal dementia, binge eating disorder, obesity, and specific genetic conditions. Neuroimaging studies have

identified several brain regions associated with abnormal functional activity in eating disorders. Lesion symptom mapping provides a unique method for identifying neuroanatomical correlates of appetite by investigating associations between brain lesion locations and post-lesion appetite change.
Methods: Multivariate lesion symptom mapping was applied to a sample of patients from the University of Iowa Lesion Registry (n=226) who suffered a brain lesion and had post-lesion neuropsychological assessment and high-resolution brain imaging. The appetite change item of the Beck Depression Inventory-II was used as the behavioral measure of interest.
Results: No brain regions reached significance for association with appetite change. However, several regions of interest trended towards a significant association with post-lesion appetite decrease, including the anterior insula and the left temporoparietal junction (r=0.10, p=0.06). Secondary analyses implicated the left amygdala as associated with appetite decrease and the basal forebrain as associated with appetite increase.
Conclusions: Lesion symptom mapping of appetite identifies candidate structures associated with appetite change when lesioned, although the strength of correlation is low.

SU16. Dissociable Control of Motivation and Goal-Directed Behavior by Distinct Ventral Striatal Dopamine Receptors

Juan Enriquez-Traba, Hector Yarur-Castillo, Rodolfo Flores-Garcia, Snehashis Roy, Ted Usdin, Rosario Moratalla, Zachary Freyberg, Hugo Tejeda*

Adaptations in goal-directed and motivated behaviors are prominent in a plethora of neuropsychiatric disorders. Thus, understanding the brain circuitry priming and maintaining these processes has important translational relevance. One of the key brain regions mediating motivation and reward-driven learning is the nucleus accumbens (NAc), a major target of dopaminergic projections from the ventral tegmental area. Dopamine D3 (D3R) and D1 receptors (D1R) are highly enriched in the NAc, and their dysregulation has been postulated as a mediator of pathophysiology in several mental health disorders. How DA receptors contribute to the development of motivation and learning within the NAc is yet poorly understood. In this study we show that D3R activity in the NAc is essential for motivated behavior, while DIRs are necessary for

goal-directed behavior in mice. Genetic ablation of D3R signaling blocked motivated behavior in three different behavioral tasks that assess motivation. This effect was also recapitulated when D3R was selectively deleted from neurons projection to the ventral pallidum (VP), lateral hypothalamus (LH) and ventral tegmental area (VTA), output regions for both D3R- and D1R- NAc medium spiny neurons (MSNs). Patch-clamp electrophysiology and optogenetics suggested that both local and efferent inhibitory transmissions to the VP are inhibited by D3R activation in a pathway-dependent manner, leading us to think that D3R action specifically in the NAc is mediating motivation. By using a combination of pharmacological antagonism and genetic ablation, we demonstrate that this behavioral output is mediated by a local D3R activation within the NAc. On the other hand, motivation was not dependent on D1R signaling in the NAc, but rather was necessary for both reward- and aversion-driven goal-directed behavior. Glutamate uncaging showed that D1 receptors might mediate this behavioral output by amplifying NMDAR-dependent responses. Collectively, our work delineates a fundamental difference in how dopamine receptor signaling in the NAc is regulated to promote dissociable behavior: D3R activation in the NAc promotes motivation by decreasing GABAergic output transmission, whereas D1R signaling is involved in enabling subsequent reward learning by promoting NMDA-dependent circuit plasticity.

SU17. Novel Mitochondrial Mechanisms Assessed in Stem Cell-Derived Neurons to Treat Bipolar Disorder and Reduce Suicide

Elizabeth Jonas, Lei Shen, Jonghun Kim, Inhyun Park, Hilary Blumberg*

Evidence implicates mitochondria in BD. Behaviorally, energy and activity changes are the first signs of acute BD episodes. Mitochondria plasticity may underlie these BD features. Patients have been noted to have increased serum and corticolimbic lactate (measured by magnetic resonance spectroscopy, MRS) and abnormal levels of nuclear and mitochondrially encoded mitochondrial transcripts. In induced pluripotent stem cells (iPSC) transformed into neurons of males (n=6) with BD, the Gage lab showed that Li+ reversed neuronal hyperexcitability and increased mitochondrial size, but the underlying mechanisms were not identified. We have now found a specific mitochondrial mechanism in stems cells from individuals with BD. The preliminary data demonstrate these abnormalities in 3 BD iPSCs sets and in two types of stem-cell derived organoids (comprised of primarily excitatory or inhibitory

neurons). We observed an abnormal increase in levels of the membrane-embedded portion of the ATP synthase (c subunit) relative to the soluble beta subunit, evidence for free c-ring. These data demonstrate an abnormality in ATP synthase assembly resulting in uncomplexed c-ring that can form a “leak” channel (ATP synthase c-subunit leak channel; ACLC) leading to alterations in cellular metabolism. The “leak metabolism” shares features with aerobic glycolytic Warburg-style metabolism and is consistent with the high lactate levels of these patients. ACLC also forms the largest pore of the mitochondrial permeability transition pore complex (mPTP) that opens under pathological conditions. mPTP is inhibited by lithium (Li+), suggesting a specific mitochondrial ion channel effect amongst Li+’s therapeutic actions in BD. Dexpramipexole (Dex) is a specific ATP synthase leak channel inhibitor that has been shown to be safe and tolerable in humans. Dex study could form the basis for the rational design of an entirely new line of therapeutics for BD, targeting ACLC and mitochondrial leak metabolism

SU18. Combined Anti-Psychotic Treatment in Acute Manic Psychosis

Bradley Tanner, Mary Metcalf*

In the treatment of acute psychosis, literature review and clinical practice reassert the common wisdom that multiple antipsychotics have a limited role. Nonetheless, acuity and urgency often necessitate trials with multiple antipsychotic agents to affect the resolution of psychosis. We specifically investigated the literature to guide the treatment of acute psychotic mania to address a severely psychotic geriatric patient requiring seclusion to avoid self-harm. In this case, trials with second-generation antipsychotics had failed and limited compliance hindered achieving proper levels of anti-manic agents. We sought to maximize the potential value of antipsychotic agents.
There is limited data on the effectiveness of third-generation antipsychotics such as aripiprazole in such a patient potentially due to up-regulation of D2 receptors (D2R). Given urgent safety concerns, we transitioned to haloperidol, a high-potency antipsychotic emphasizing selective D2R full antagonism. We optimized treatment with haloperidol until EPS hindered further adjustment despite typical EPS interventions. To proceed, we investigated adjunctive medications with multiple trials and this necessitated focusing on medications with longer-term usage and multiple investigations. Given aripiprazole's partial dopamine

D2R agonism and haloperidol's selective dopamine D2R full antagonism the combination was the most logical to consider. In fact, haloperidol value alongside aripiprazole has been reported for emotional dysregulation, treatment-resistant schizophrenia, and antipsychotic-Induced hyperprolactinemia. After adding aripiprazole at a low dose, despite weeks of uncontrolled mania on an inpatient basis, the psychosis resolved. Safety measures could be discontinued and compliance improved sufficiently to achieve proper anti-manic medication levels. Our experience mirrors others who emphasize the usage of a high potency typical antipsychotic to its most reasonable dose followed by low dose partial agonist such as aripiprazole at a low dose. A potential explanation is the countering role of aripiprazole's stronger binding affinity toward D2R and slower dissociation kinetics versus haloperidol. Although the proper dose requires further investigation; in our case a low dose was sufficient.

SU19. Identification of Dysregulated Micro-RNAs in Human Brain Tissue From Psychiatric Patients

Erik Kaadt, Lasse Sommer Kristensen, Birgitte Mumm, Jørgen Kjems, Betina Elfving*

The diagnosis of depression is made through clinical examination and based only on symptoms. This is problematic as symptoms are partly overlapping in bipolar disorder, schizophrenia, and depression. Clinical observations have also reported gender differences in prevalence, symptoms, and responses to treatment. Although progress has been made in recent years to understand the molecular mechanisms underlying depression, the knowledge is still limited. There is thus a need for biomarkers and molecular insights into depression, which allow for a more precise diagnosis and personalized treatment.
Recently, it has been demonstrated that alterations in gene-expression profiles are associated with depression and that translation-efficiencies imposed by some non-coding RNAs, such as microRNAs (miRNAs), play central roles in disease etiologies. Here, we investigate transcriptional patterns of miRNAs in human brain tissue (FFPE blocks of polus frontalis (n=132) and hippocampus (n=119)) from the Danish Brain Collection (Risskov). Males and females diagnosed with schizophrenia, bipolar disorder, and depression were included. As an unbiased profiling strategy, we utilized the Nanostring technology to investigate miRNA expression in the brains. We have previously reported that Nanostring is more accurate

and sensitive than Next-Generation-Sequencing on FFPE samples for miRNA-detection. The results demonstrated both gender- and disorder-specific differences in miRNA-expression.

SU20. MRI Quantification of Ophthalmic and Brain Structural and Physiologic Changes Due to Long-Duration Spaceflight

Katherine Warthen, Gabryel Conley Natividad, Stuart Sater, Larry Kramer, Khader Hasan, Brandon Macias, Steven Laurie, Laura Pardon, Bryn Martin*

Introduction: Long duration spaceflight (LDSF) has several effects on the nervous system, including potential changes in white matter (WM) volume, gray matter volume, ventricular volume, cerebrospinal fluid flow, optic globe volume structural changes, and optic nerve (ON) and sheath area. Here, we evaluate these measures in a cohort of LDSF astronauts and a group of control participants to quantify measurement repeatability and variation.
Methods: MRI scans were collected from a control cohort not exposed to microgravity (N=10) at baseline, 2, 6, and 12 months. The cohort of LDSF astronauts (N=10) underwent MRI collection pre- and return (R+3 days) LDSF with an average time in space of 6 months. Post-processing of the optic images and quantification of posterior globe volume displacement was conducted in an identical manner as previously described by Sater et al. [1]. Pulse-gated MRI phase-contrast flow imaging was used to quantify peak-to-peak cerebral spinal fluid (CSF) velocity (CSFVp-p) within the cerebral aqueduct. A 3D T1-MPRAGE sequence was used to quantify total intracranial volume (ICV = brain and intracranial CSF spaces) using MRI Cloud software.
Results: Control participants had no significant changes in globe volume displacement (-1.92±4.99, -4.50±3.65 and -0.61±6.41 mm3 at 2, 6 and 12 months, mean±STD), ON (11.31±1.85, 10.85±2.48, 10.89±2.25, 10.77±2.55 mm2), ONS (28.92±10.92, 30.29±10.9, 28.93±10.83, 30.56±11.55 mm2 at 0, 2, 6 and 12 months, mean±STD), CSFVp-p (12.2±.3,2, 12.9±4.5, 12.2±3.1, 11.0±4.0 mL) or ICV (1466±133, 1481±141, 1465±131, 1482±141 mL). In contrast, LDSF astronauts showed greater globe volume displacement (11.09±11.30, $p=5.3 \times 10^{-5}$) but did not have significant changes in ON (10.639±1.68, preflight; 11.209±2.24, post, $p>0.05$) or ONS (30.385±8.08, preflight; 31.04±7.09, post, $p>0.05$). The astronauts showed increased mean volumes in the brain (28 mL, $p<0.001$), WM (26 mL, $p<0.001$), ventricles (2.2 mL, $p<0.001$), ICV (33mL,$p<0.001$), and CSFVp-p(2.2 cm/s,$p=0.01$) [2].

Conclusion: These findings support that MRI-based globe volume displacement is relatively consistent over a 12-month period in healthy controls and that changes in ocular globe volume displacement, brain volumes, and CSF flow rate is typically present after LDSF.

SU21. Locally Sustained Interactive Oscillations in a Quantitative Neural Population Model

Yu Qin, Ipshita Zutshi, Alex Sheremet*

A basic question in understanding collective spiking patterns that emerge in a neural population is whether these patterns are locally sustained or driven by external forcing. A prior experiment shows that silencing the medial entorhinal cortex (mEC) largely abolished extracellular theta and gamma currents in CA1 but the firing rates persist. In contrast, CA3 and local CA1 silencing strongly decreased firing of CA1 neurons without affecting theta currents (Zutshi et al. 2022).
To gain insights into potential mechanisms of CA1 firing rate maintenance and the co-emergence of theta and gamma, we simulate a neural population model that mimics the CA3-CA1 circuits (Qin et al. 2022, also poster presented at WCBR22). Interestingly, the model shows that spiking rate can be weakly sustained by local interactions within recurrent excitatory and inhibitory populations, while amplitudes and frequencies of the synchronized activity patterns can be modulated by external forcing. The model simulations show that the recurrent excitation in CA3 can be weakly self-sustained and thus is a major contributor to maintaining the spiking rate in CA3-CA1 circuits. The resonant frequency of CA3 recurrent excitatory connections is in the theta frequency band, and the resonance can be activated and amplified by external forcing. This means that external input into CA3 plays a crucial role in arousing the resonance instead of directly energizing the firing activities. The resonance mechanism also occurs within CA1-mEC circuits, however, the strength of the looped connections is not strong enough to maintain the firing rates in either CA1 nor mEC. Therefore, the mEC inputs into CA1 play the role of reorganizing the strength of resonance instead of maintaining the firing rate.
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Qin, Yu, and Alex Sheremet. "Mesoscopic Collective Activity in Excitatory Neural Fields: Governing Equations." arXiv preprint arXiv:2206.07966 (2022).

SU22. Computational Modeling of the Processes Underlying Cognitively Effortful Decision Making in Rats

Claire Hales, Mason Silveira, Brett Hathaway, Leili Mortazavi, Sebastian Wittekindt, Wendy Adams, Catharine Winstanley*

Decision making often involves determining whether the cognitive effort required is worth it for the desired outcome. Motivational deficits and inappropriate use of attentional resources during decision making are common features in most psychiatric illnesses. The rat Cognitive Effort Task (rCET), a rodent model of cognitive rather than physical effort, is a cognitively demanding attentional task where animals choose between an easy or hard visuospatial discrimination, with a correct hard choice more highly rewarded. Within a population of rats, like in humans, there is stable individual variation in choice behavior, whereby “workers” choose hard trials significantly more than their “slacker” counterparts. Previous work has shown that serotonergic drugs (four different receptor subtype agonists and antagonists) alter impulsivity and accuracy on the task, but have little effect on choice for the more cognitively effortful hard option. Conversely, a cholinergic drug, scopolamine, reduces animals’ choice for the hard option in workers, but has no effect on accuracy or impulsivity. Here, we use the drift diffusion model, a two-choice cognitive model that maps components of the decision-making process onto psychologically meaningful parameters, to further probe task performance in workers and slackers, and the differences underlying the pharmacological dissociation. Fitting the model to behavioral data from the rCET revealed that workers have higher values for parameters linked to response caution (decision threshold) and, unsurprisingly, integration of preference for the hard versus easy choice (drift rate). Serotonergic drugs alter the decision threshold parameter and the length of time attributed to non-decision processes, whilst scopolamine’s effects are due to changes in drift rate, as well as shifting a priori bias for one or other choice (decision starting point). These results provide insight into the mechanisms through which different neurotransmitter systems impact cognitively effortful decision making.

SU23. The Gut Microbiome Modifies Risky Decision-Making After Traumatic Brain Injury, Potentially via Serotonin

Kris Martens, Noah Bressler, Michelle Frankot, Kristen Pechacek, Carissa Gratzol, Michael Bailey, Cole Vonder Haar*

Traumatic brain injury (TBI) causes cognitive impairment, increases psychiatric disease, and augments related symptoms such as risky decision-making and impulsivity. Impaired monoamine neurotransmission is a likely contributor to such symptoms, with serotonin signaling contributing to anxiety and mood-related disorders, impulsive dysfunction, and impaired decision-making. Despite this knowledge, precisely why these systems are vulnerable to TBI is unknown. However, emerging data indicate a role for the gut microbiome. Gut dysbiosis, or an imbalance in microbial populations, occurs rapidly after TBI and may persist for years in patients. Dysbiosis is correlated with outcome severity in post-injury patients and animals. The current study sought to evaluate the contributions of gut dysbiosis to impulsivity and risky decision-making. In the first experiment, we evaluated the degree to which gut dysbiosis disrupted serotonin synthesis using qPCR to quantify L-type amino acid transporters 1 and 2 and HPLC/MS for targeted analysis of metabolites along 5-HT synthesis pathways. The results from this experiment showed decreases in serotonin transmitter levels at 24 hours, 72 hours, and 7 days following frontal TBI; however, no differences in amino acid transporters. In the second experiment, we manipulated the microbiome using antibiotic dysbiosis and assessed function on the Rodent Gambling Task, a clinically-relevant assessment of impulsivity and decision-making. In this study rats were administered an antibiotic cocktail for 3 weeks prior to frontal TBI. Following TBI, rats were tested on the RGT. The results of this experiment showed that the antibiotic cocktail delayed onset of TBI symptoms. Taken together, the findings from this study show that TBI reduces brain serotonin levels without altering amino acid transporters in the gut. The findings also show disruption of the gut microbiome (via antibiotic cocktail) prior to frontal TBI leads to functional sparing on an assessment of impulsivity and decision-making.

SU24. Distinct VTA Glutamatergic Populations Differentially Signal Reward Value and Economic Decision Making

Dillon McGovern, Kayla Siletti, Emily Prevost, Annie Ly, David Root*

The Ventral Tegmental Area (VTA) is a cellularly heterogeneous midbrain region that contributes to drug-seeking, reinforcement learning, stress, and motivated behavior. Previous literature has established that VTA dopamine neurons, defined by the expression of tyrosine hydroxylase (TH), are recruited for consummatory reward behaviors as well as reward value judgments and economic decision making in mice. However, recent data implicate glutamate neurons, defined by the expression of vesicular glutamate transporter 2 (VGluT2), in reward as well. Several subtypes of VGluT2 neurons intermingle within the VTA but their contributions toward reward are unknown. In these projects we used a combination of transgenic mice and intersectional or subtractive viral monitoring and manipulation strategies to characterize the contribution of 1) VTA VGluT2+VGaT+ neurons 2) VTA VGluT2+VGaT- neurons 3) and VTA VGluT2+TH+ neurons to consummatory reward value and motivated behavior. Mice were injected with GCaMP6m respective to the cell-type of interest and were recorded using fiber photometry during a two-bottle choice consummatory reward task (sucrose, fat, saccharine). Escalating concentrations of sucrose were used to assess neuronal responses to changes in reward value. VTA glutamate cell-types, regardless of neurotransmitter co-expression, scaled calcium signaling relative to sucrose concentration. Behaviorally mice developed a preference for fat consumption over sucrose but interestingly the recorded calcium change for fat was significantly less in the VGluT2+VGaT+ population. The VGluT2+VGaT- population signaled more robustly for fat than sucrose, which suggests that subjective reward value may be more salient for this population of neurons. We adapted a behavioral economic paradigm to assess the causal role of VGluT2+VGaT+ co-expressing neurons in sucrose reward valuation. We artificially manipulated reward price by reducing the amount of sucrose delivered as the program elapsed to devalue effort for reward. Optical stimulation of VTA VGluT2+VGaT+ neurons increased responding for reward at higher price compared to controls. Further, this project provides novel insights into the functional contributions of genetically-distinct VTA glutamatergic cell-types in reward processing.

SU25. Decoding the Molecular Computation by CaMKII Holoenzymes That Directs Synaptic Plasticity

Carolyn Brown, Steven Coultrap, Kevin Crosby, Steve Reichow, Ulli Bayer*

Learning, cognition, and memory require dynamic remodeling of hippocampal synapses, which in turn requires

Ca2+/calmodulin-dependent kinase II (CaMKII). CaMKII directs two opposing modes of synaptic plasticity, long term potentiation (LTP) and depression (LTD), that are induced by distinct Ca2+ stimuli. Both low and high [Ca2+] induce CaMKII autophosphorylation (p) at T286, that is required for both LTD and LTP. LTP additionally requires CaMKII binding to the NMDA receptor subunit, GluN2B; LTD instead requires additional CaMKII autophosphorylation at T305/306. Further, these three mechanisms undergo cross-regulation between the 12 subunits within CaMKII holoenzymes. It is unknown, however, how these reactions and interactions are spatiotemporally encoded within holoenzymes and thus how LTP versus LTD signal computation is accomplished by CaMKII. For example, it has been shown that pT286 must occur between two neighboring kinase domains in a holoenzyme. Still, it is unclear what determines a functional kinase domain neighbor. Moreover, in vitro binding studies have shown that CaMKII holoenzymes are required for binding to GluN2B, suggesting that this interaction may require multiple subunits. Still, it is unknown what is the required stoichiometry and subunit geometry required for CaMKII-GluN2B binding. To this end, we have developed several CaMKII holoenzyme fragments with altered quaternary structure. Initial biochemical experiments with these fragments suggest that the holoenzyme rules for pT286 and GluN2B binding are fundamentally different. We hypothesize that LTP versus LTD mechanisms are regulated by structurally distinct features within CaMKII holoenzymes. Our results provide insight into how molecular signal computation underlying the LTP versus LTD decision is encoded within CaMKII holoenzymes.

SU26. Utilization of Remote Aerobic Exercise Monitoring to Facilitate Exercise Adherence in People With Parkinson's Disease

Anson Rosenfeldt, Elizabeth Jansen, Cielita Lopez-Lennon, Erin Suttman, Kelsey Owen, Leland Dibble, Jay Alberts*

Purpose: Current recommendations call for individuals with Parkinson's disease (PD) to engage in 90-150 minutes of aerobic exercise per week. In-home, commercially available platforms may eliminate some exercise barriers. As part of an on-going randomized clinical trial (NCT04000360), individuals with PD were asked to cycle 3x/wk for 12 months on an in-home stationary cycle (Peloton Interactive, New York, NY). The purpose of this project was to evaluate the feasibility of using a commercially available exercise platform to facilitate exercise adherence and

progression.
Participants: To date, 96 individuals with PD have completed the 12-month exercise intervention.
Methods: Data from each ride were stored on the Peloton platform and examined weekly. Successful implementation of monitoring of exercise behavior was defined as the ability to gather summary exercise performance data (e.g., ride duration (min), cadence (rpm), workload (kJ), and heart rate (bpm). Visual examination and data filtering techniques were implemented to ensure the rides were complete. During bi-weekly 1:1 phone calls with participants, the exercise prescription was progressed by a physical therapist based on objective performance variables and participant feedback.
Results: 13.7% of the rides were less than 5 minutes and were classified as a warm-up or cool-down rides. Additionally, 3% of the data were incomplete, indicating a ride was initiated but not finished. Following the removal of the aforementioned rides, 96 PD participants completed 13,752 aerobic exercise sessions over 12 months (mean 143.3 (53.9) rides/person). Exercise duration increased from Week 1 (78.1 (44.3) min) to Week 5 (92.0 (52.6) min) to meet the aerobic exercise recommendations and was largely maintained throughout the 12-month duration.
Discussion: The high level of adherence and achievement of aerobic exercise recommendations indicates a commercially available, in-home platform and use of its data provided a mechanism to overcome common barriers preventing individuals with PD from engaging in aerobic exercise. The model of exercise delivery and progression could be integrated into a remote monitoring and care model for PD clinical care to aid in the meeting of aerobic exercise recommendations to facilitate the potential medicinal effects of exercise.

SU27. The Impact of Blood-Brain Barrier Modulation by Focused Ultrasound on Oligodendrogenesis

Kate Noseworthy, Joseph Silburt, Rikke Hahn Kofoed, Kullervo Hynynen, Isabelle Aubert*

Introduction: Alzheimer disease (AD) is characterized by proteinopathy and the degeneration of neurons and oligodendrocytes (OL). Strategies aimed to enhance oligodendrogenesis show improved cognition in mouse models of amyloidosis. However, these approaches fail to address other pathologies of AD (e.g. tau, Aβ, neuroinflammation) which remain

critical to establishing a multi-modal therapy. Based on the knowledge that focused ultrasound combined with intravenously-injected microbubbles (FUS) increases the plasticity of neurons and glia, we aimed to establish the effects of FUS on OLs and their precursors. Specifically, we hypothesise that FUS, and the associated modulation of the blood-brain barrier, will enhance oligodendrogenesis.
Methods: FUS was targeted to the hippocampus and striatum of adult mice. Using immunohistochemical procedures, we investigated the proliferation oligodendrocyte progenitor cells (OPCs) and their differentiation. The activation of glial cells is known to influence oligodendrogenesis through the secretion of cytokines, chemokines, and growth factors. Thus, we evaluated glial activation following FUS using a machine learning workflow, MORPHIOUS
Results: FUS promoted the proliferation of OPCs in the hippocampus by 5- and 2-fold at 1 and 4-days post-FUS, respectively, and led to a 5-fold increase in total number of OPCs generated between 1 and 7 days post-FUS in the striatum. Oligodendrogenesis, defined by newly dividing OPCs maturing into OLs was promoted by 5- and 6-fold in the hippocampus and striatum after 30 days, respectively. Finally, we explored the relationship between glial activation and OPC proliferation.
Conclusion: Our results support FUS as a strategy to expand the endogenous OPC population and promote oligodendrogenesis. The non-invasive nature of FUS combined with its established functions of reducing A pathology and promoting regeneration position FUS as a multi-modal approach to address multiple aspects of AD pathology.

SU28. Lysosomal Lipid Accumulation in Neurons Promotes Early Alzheimer's Pathology by Preventing Lysosomal Clearance of Intraneuronal Aβ1-42

Alexandra Barnett, Jian Zou, Lamar Dawkins, Meagan Colie, Lauren Larison, Aaron Rohlman, Leon Coleman*

Alzheimer's (AD) features the progressive accumulation of pathological amyloid and tau species. We sought to identify shared underlying cell biological vulnerabilities that promote early AD pathology. We hypothesized that two common modifiable risk factors for AD, heavy alcohol use and obesity would promote early intraneuronal Aβ1-42 through loss of autophagy. Triple transgenic AD mice (3xTg-AD, APPSwe, tauP301, Psen1tm1Mpm) received either chronic or a western diet with assessment at 11 months of age, prior to maximal AD pathology and

cognitive deficits. Chronic heavy alcohol and obesity each increased intraneuronal Aβ1-42 and phosphorylated tau species in both sexes. Similar to findings in 3xTg-AD mice, human subjects with alcohol use disorder had increased levels of early AD-associated phosphorylated tau isoforms in the frontal cortex and the hippocampus along with increased Aβ1-42 in frontal cortex. In 3xTg-AD mice, both ethanol and obesity reduced autophagic flux (increased P62, reduced Beclin) and caused lysosomal dysfunction (reduced TFEB, lysosomal acid lipase/LAL, and vATPases). Further, expression of genes that regulate lipolysis (PPARα, hormone-sensitive lipase), and lipid efflux (ABC transporters) were also reduced. Lysosomal lipid accumulation was found in neurons and was positively correlated with intraneuronal Aβ1-42. Also, the ratio of lysosomal to cytosolic Aβ1-42 was significantly reduced and negatively correlated with neuronal lysosomal lipid levels, suggesting lipid accumulation in neuronal lysosomes prevents lysosomal clearance of Aβ1-42. Thus, two common modifiable risk factors for sporadic AD may promote early AD pathology by causing accumulation of lipid in neuronal lysosomes that prevents lysosomal degradation of intraneuronal Aβ1-42.

SU29. Modal Analysis of Natural Vibration Frequencies of the Brain and Head

Turner Jennings, Rouzbeh Amini, Sinan Müftü*

Physical structures in the absence of outside forces tend to vibrate at specific natural frequencies. If an outside vibration is applied with a frequency equal to one of the structure's natural frequencies, it induces potentially harmful resonance in the structure, leading to a larger vibration amplitude than the input force. Quantifying the natural frequencies of a structure, whether it is manmade or not, is critical in identifying vibration sources which may be harmful to it. In this study, we used an anatomically faithful computational model to characterize vibration frequency ranges that may induce potentially harmful resonance in the brain and head.
The natural frequencies of the brain and head were calculated by modal analysis using the finite element method. This analysis was performed using the Total Human Model for Safety (M. Iwamoto Et Al., 2015), a computational human body model which includes a fine-detail model of the head. The material properties of the head are simplified to linear elastic or viscoelastic models to allow calculation of the natural

frequencies. The first 10 natural frequencies were calculated for the brain alone, brain with Cerebrospinal Fluid (CSF) and meninges, skull alone, and full head. The first 10 natural frequencies of these structures were calculated as 1.1-6.1 Hz, 12.6-16.0 Hz, 1026.2-2301.3 Hz, and 11.2-14.5 Hz respectively. The vibration modes for the full head model show flexion and rotation concentrated at the white and gray matter of the brain. Exposure to this range of frequencies occurs regularly in automotive and industrial settings.
This study lays the foundation for further investigation into the effects of tissue properties or subject-to-subject variation on natural frequencies, as well as further investigation into cellular-level response to these vibration frequencies.

SU30. Detailed Mapping of Stroke-Induced Molecular Changes in a Mouse Model Using Spatially Resolved Transcriptomics Approach

Tianyu Zheng, María Pedraza, Emma Gerrits, Nicholas Mitsios, Evelina Husén, Ulrika Wilhelmsson, Marcela Pekna, Ning Liang, Zhouchun Shang, Turgut Tatlisumak, Jan Mulder, Milos Pekny*

Stroke is characterized by cellular disturbances that involve disruption of blood-brain barrier (BBB), inflammation, oxidative damage, and neurodegeneration. Intracerebral hemorrhage (ICH) accounts for 15%–20% of all strokes and, although it is less frequent than ischemic stroke, it is associated with much higher morbidity and mortality. Despite recent improvements in minimizing ICH-associated brain damage, the molecular changes and cellular interaction of stroke-induced neuronal death are not yet fully understood. Since bulk RNAseq studies average tissue gene expression, scRNAseq investigates gene expression of individual cells, spatially resolved transcriptomic technologies are promising tools that reached subcellular resolution, enabling detailed analysis of individual cells within their environment, providing biological insights in complex disease processes and the gradient of cell-cell interactions around a lesion site in stroke. Here, we present the first detailed spatial transcriptomic analysis of an adult mouse ICH model. Spatial enhanced resolution omics-sequencing (Stereo-seq) technology combines DNA nanoball (DNB)-patterned arrays (500 nm interval) and in situ RNA capture to explore the transcriptomic landscape of the brain. In our study, mice were unilaterally injected with collagenase to induce hemorrhagic stroke. After 48-hour survival, mice were sacrificed, and brain tissue processed for stereo-seq analysis. In our result, each 10 μm section

provides us ~150 M unique reads, and ~1000 genes were detected within 50 Í 50 bin (225 m2). Unsupervised clustering analysis of bins revealed 26 distinct clusters of which 6 were associated to the lesion. Projecting these clustered bins on the tissue section revealed tissue domains within the healthy and stroke affected tissue characterized by cellular composition and molecular responses to damage. A comparison of the ipsilateral with the contralateral hemisphere has provided lists of deregulated genes for each cell type, that can be explored to identify molecular dynamic changes and stroke associated genes in the hemorrhagic brain. Furthermore, with high-resolution location information, it is possible to untangle the dysregulated cellular network in the vicinity of pathogenic hallmarks of ICH.

SU31. Development of Drug Resistance in Seizure Suppression With Long Term MTOR Inhibitor Treatment in a Mouse Model of TSC

*Luis Martinez, Vishnu Susheer, Wai Ling Lee, Anne Anderson**

Tuberous Sclerosis Complex (TSC) is a genetic disorder characterized by brain malformations and severe epilepsy in up to 90% of patients. Mutations in TSC1 or TSC2 genes result in dysregulation of the mTOR pathway and TSC. mTOR inhibitors can reduce seizures in some TSC patients, but may not have a disease modifying effect. Here we treated a mouse model of TSC with the mTOR inhibitor RAD001 and tracked EEG and mTOR activity. Littermate pups with conditional forebrain deletion of the Tsc2 gene in excitatory neurons [Wild type, (WT) NEX-Cre+/Tsc2WT/WT; Knockout (KO), NEX-Cre+/Tsc2flox/flox] were treated with vehicle or 6mg/kg RAD001 by intraperitoneal route every other day beginning postnatal day 8 (P8). Video electroencephalography (vEEG) was started on postnatal day 10 (P10). EEG analysis of epileptiform and seizure activity was performed. mTOR signaling was evaluated using western blotting of cortical tissue harvested from the treated animals at various time points. Phospho-S6 (pS6) levels were assessed as a readout of mTOR kinase activity. vEEG revealed that Tsc2 KO mice exhibit epileptiform activity and severe seizures during the second postnatal week that result in early mortality. KO mice treated with RAD001 early in development prolonged survival ($p<0.01$) and delayed onset of seizures to P50. pS6 levels were significantly reduced and comparable to vehicle treated WT ($p>0.05$) to P35 but levels significantly increased at P45 ($p<0.05$). Our results in NEX-Tsc2 mutant mice indicate that, as in TSC humans, mTOR inhibition suppresses epileptiform activity but does not render a long-lasting disease modifying effect.

Molecular studies are underway to evaluate mechanisms of drug resistance in this model with potential translational relevance. Funding: DoD

SU32. Highly Localized Dopamine Signals Evoke Post-Synaptic Responses in Striatal Medium Spiny Neurons

Andrew Yee, Chris Ford*

Dopamine (DA) signaling is commonly thought to be mediated by volume transmission, whereby low concentrations of the transmitter non-selectively activate extra-synaptic DA receptors after its diffusion from distant release sites. However until recently, existing tools have limited our ability to resolve spatial, temporal and concentration dynamics of DA signaling. Using a combination of two-photon imaging of a genetically-encoded DA sensor and whole-cell electrophysiology, we have defined the 'minimal unit' of DA transmission onto medium spiny neurons (D2-MSNs) in striatal brain slices. Sparse activation of only a few active zones on SNc axons evoked spatially-restricted DA release which produced 'minimal' D2 receptor-mediated inhibitory post-synaptic currents (min. D2-IPSCs). These responses could be mimicked by focal application of a high, but not a low concentration of exogenous DA, confirming that receptor activation requires high concentrations of DA. Stimulation of DA release at different dendrites on the same MSN, often failed to evoke post-synaptic responses, indicating that post-synaptic specializations likely exist where responses could be produced. Taken together, our data suggest that there is greater organization between DA release sites and the dendrites of D2-MSNs than previously assumed, providing an additional mechanism for spatially-precise encoding of DA signals in the striatum.

SU33. Scanned Line Angular Projection Two Photon Laser Scanning (SLAP2) Microscopy for Real-Time (Kilohertz Rates) Volumetric in Vivo Imaging at Subcellular Resolution

Aidan E. Sullivan, Jacob R. Glaser, Bruce Kimmel, Georg Jaindl, Paul J. Angstman, Kaspar Podgorski, Daniel A. Flickinger, Nicolas Roussel, Jonathan King*

Calcium imaging has been the gold standard for functional in-vivo imaging of neural activity. However, calcium imaging lacks the temporal resolution to capture the fast transients of action potentials in neurons. Although new fluorescent voltage and neurotransmitter indicators, such

as Voltron, have been developed to overcome this limitation, the emerging labeling mechanisms require new imaging methods to capture neuronal activity at kilohertz rates. SLAP2 microscopy uses a novel and unique scan technology where a vertical laser line is horizontally swept nearly 10,000 times per second across the surface of a digital micromirror device (DMD) that projects excitation light to regions of interest (ROI) within the optical field of view (FOV). Capable of imaging in vivo mouse brain and in vitro brain slices at subcellular spatial resolution, the microscope can be used to capture the activity of multiple cell body-sized volumetric ROIs scanned at kilohertz rates. The DMD switches individual pixels in a FOV “on" and “off" at full scan rates, allowing random-access imaging of ROIs with minimal mechanical movement overhead, increasing imaging speeds by roughly 30x that of a resonance scanning 2-photon microscope.
Preliminary raster scanning images of glutamate signals acquired in-vivo from excitatory neurons in the mouse visual cortex in the laboratory of Dr. Podgorski have validated that the SLAP2 technology can detect transience in synaptic activity. Going forward we plan to extend this concept and validate the system’s ability to image with kilohertz scanning rates by employing fast ROI scanning methods. Other goals include continuous improvement of the SLAP2 prototype through hardware refinements and developing software to increase reliability and performance. We intend to accomplish this through implementation of motion correction functionality, automated cell segmentation and ROI definition features. With a temporal resolution of milliseconds (i.e., 1000 Hz and higher), we believe that SLAP2 will enable many experimental paradigms focused on imaging living neuronal circuits. The fast, large-scale microscopic imaging advancement will also expand our ability to accurately characterize physiological activity in three-dimensional culture and organoid models.

SU34. Brainwide Tracing of Monosynaptic Inputs to Ventral Tegmental Area Glutamate-Gaba Co-Transmitting Neurons

Emily Prevost, Alysabeth Phillips, Kristoffer Lauridsen, Dillon McGovern, Connor McNulty, Yoon Seok Kim, Lief Fenno, Charu Ramakrishnan, Karl Deisseroth, David Root*

The ventral tegmental area (VTA) is a heterogenous midbrain structure involved in the processing of motivated behaviors. With the advent of

INTRSECT viral vectors allowing specific targeting of neurons defined by multiple genetic characteristics, the roles of molecularly diverse VTA cell-types have begun to be dissected. The recently discovered glutamate and GABA co-transmitting VTA neurons signal rewarding and aversive outcomes. However, the pattern of neuronal integration onto this unique population of cells is heretofore unknown. Using a genetically modified mouse line that expresses Cre recombinase in cells expressing vesicular glutamate transporter type 2 (VGluT2) and Flp recombinase in cells expressing vesicular GABA transporter (VGaT), we have mapped brainwide synaptic inputs to glutamate-GABA co-transmitting neurons in the VTA. We infused eight VGluT2::Cre/VGaT::FlpO double transgenic mice with Cre- and Flp-dependent helper viruses (AAV8-nEF-Con/Fon TVA-mCherry and AAV8-Ef1a-Con/Fon oG) followed by a monosynaptic retrograde rabies virus (EnvA-ΔG rabies-GFP). Via high-throughput imaging and a novel tool for semi-automated brain registration (SHARCQ), we quantified the presynaptic input neurons by brain region according to a mouse brain atlas. Glutamate-GABA VTA neurons received the most inputs from the lateral hypothalamus, superior colliculus, periaqueductal gray, lateral habenula, VTA, and dorsal raphe. Cell-type identification and functional assessments of presynaptic neurons are ongoing and will be discussed at the meeting.

SU35. Research Opportunities From the Archived Neuroanatomic Slide Collections of the National Museum of Health and Medicine

Daniel Perl, Archibald Fobbs, David Priemer, John Morris*

In past years, researchers created very large collections of serial whole mount histology brain slides. Many of these archival collections were donated to the US Government and are housed at the National Museum of Health and Medicine, Silver Spring, MD. Currently, the only way for researchers to use these precious slides has been to travel to Maryland and physically examine them onsite. Nevertheless, over the years these collections have been widely used and a number of seminal publications have emerged from this unique resource. However, we are now proposing to digitize these entire collections and make them widely available through on-line internet access. The collections being considered for this project are as follows: 1) Yakovlev Collection consisting of 1200 serially cut human brain specimens (250,000+ slides, Nissl and myelin serial sections representing normal, and many pathologic entities). 2) Welker Comparative Neuroanatomy Collection: serial sections of 275 brains

representing over 120 species (aardvark to zebra). 3) Starr Collection containing serial sections of brains of chimpanzees and gorillas. 3) Meyer Collection with serially sectioned slides from the brains of patients seen by psychiatrist Dr. Adolph Meyer who practiced at Johns Hopkins Hospital in the early part of the 20th century (including his clinical note), and the Blackburn Collection with neuropathology evaluations of St. Elizabeth's Hospital cases dating back to 1884. Both the Meyer and Blackburn collections date from the pre-antibiotic era with numerous examples of unique pathologic entities, (e.g. various forms of neurosyphillis, catatonic schizophrenia, etc.). Examples of these holding will be displayed and we will provide an on-line demonstration of the opportunities available to researchers for dealing with this material in a digitized format.

SU36. Correlation Between Subcutaneous Adipose Tissue of the Head and Body Mass Index: Implications for Functional Neuroimaging

Stacey Gorniak, Hao Meng, Luca Pollonini*

High body mass index (BMI) is generally assumed to represent overall amounts of body adipose tissue (fat). Increased adipose tissue amounts in persons with increased BMI has been cited as a barrier to assessment of body tissues such as muscle. Significant increases in the amount of adipose tissue between the dermal layer and the skull may result in high electrical impedance and/or increased light diffusion causing a lower signal to noise ratio during use of neuroimaging tools such as electroencephalography (EEG), transcranial direct current stimulation (tDCS), and functional near infrared spectroscopy (fNIRS). Investigating how subcutaneous adipose tissue in the head region increases with respect to total body fat percentage and BMI is an important step in developing mathematical corrections in neuroimaging measurements as BMI increases, as recommended in other measurement modalities such as electromyography (EMG). We hypothesized that percentage of subcutaneous adipose tissue in the head region would increase with respect to both total body fat percentage and BMI. A statistically significant increase in subcutaneous head fat percentage occurred with increased BMI and total body fat percentage. The data investigated in this study indicate that participant age, sex, and BMI are important features to consider in model corrections during data signal processing and analyses for subcutaneous head fat in neuroimaging approaches. The data in this project serve to provide physiological justification for this practice along with regression analyses to be considered for physiologically-based signal to noise correction algorithms.

SU37. JNK Signaling Dose and Sex-Dependent Effects on CP55,940 Tolerance to CB1 Desensitization-Resistant Mutant Mice

*Melissa McHann, Isabel Castro-Piedras, Daniel Morgan, Josee Guindon**

Introduction: Studies from our group and others have found sex-differences in the response to cannabinoid compounds (Blanton et al., 2021). Chemotherapy-induced peripheral neuropathy (CIPN) is a clinical challenge for cancer patients. The development of novel targeted therapies with long-term efficacy in alleviating CIPN is an ongoing focus of preclinical research. However, our current understanding of the mechanisms underlying tolerance to cannabinoid compounds remains elusive as does the contribution of sex differences to this process.
Methods: The objective of our current work is to assess in S426A/S430A female and male mutant mice whether JNK (SU 3327) inhibitor, CP55,940 (mixed CB1/CB2 receptor agonist) alone or in combination demonstrate sex-specific antinociceptive effects and delay in the development of tolerance using cisplatin (5 mg/kg/week) as a CIPN model. We also evaluated co-immunoprecipitation of JNK1 and JNK2 with β-arrestin 2 in HEK293-CB1 cells.
Results: Our study found that SU 3327 (3 mg/kg i.p.) partially reversed mechanical (von Frey) and cold (acetone) allodynia in male and female KI mice from day 8 to day 35. However, this effect was not observed at a lower dose of SU 3327 (1 mg/kg i.p.). When low dose SU 3327 (1 mg/kg i.p.) was combined with CP55,940 (0.3 mg/kg i.p.), there was a delay in the development of tolerance to the effects of CP55,940 on mechanical and cold allodynia in female mice. Indeed, tolerance to the effects of CP 55,940 on mechanical allodynia developed on day 28 for CP55,940 alone and on day 33 for SU 3327 + CP55,940 for female KI mice. Tolerance to effects of CP55,940 on cold allodynia developed on day 27 for CP55,940 alone and on day 32 for SU 3327 + CP55,940 for female KI mice. For male KI mice, tolerance to the effects of CP55,940 on mechanical and cold allodynia developed on day 33 and on day 32 for CP55,940 alone or combined with SU 3327, respectively. To better understand a possible mechanism for these findings we performed co-immunoprecipitation experiments and found that JNK2 and β-arrestin 2 form a complex in CB1-espressing HEK293 cells.
Conclusions: Our results illustrate the important role of sex in the development of cannabinoid tolerance in the context of chronic pain and the contribution of sex-specific mechanisms of action

Monday, January 23, 2023

POSTER SESSION III
3:30 PM – 4:30 PM
BALLROOMS 2 & 3

M1. D-Cysteine Ethyl Ester Disrupts Acquisition of Fentanyl Seeking While Preserving Fentanyl-Induced Motoric and Analgesic Efficacy

*Zackery Knauss, Caden Hearn, Stephen Lewis, Devin Mueller**

Opioid overdose results in Opioid-Induced Respiratory Depression (OIRD) which is treated by administration of competitive opioid receptor antagonists such as naloxone. However, these drugs are not as effective against highly potent synthetic opioids, particularly fentanyl, and can trigger severe withdrawal symptoms. Recently, D-Cysteine ethyl ester (D-CYSee) has been shown to prevent OIRD without affecting analgesia or inducing a withdrawal state in rats. Thus, we assessed the effects of D-CYSee administration on the acquisition of fentanyl-induced seeking behaviors, anxiety, and locomotion using a rat model of conditioned place preference (CPP) and open field testing (OFT). Long Evans rats underwent place conditioning in a three-chamber apparatus for eight days under: 1) saline (1 ml/kg, i.p.) - fentanyl (male 5 ug/kg / female 50ug/kg, s.c.), 2) D-CYSee (10 mg/kg, i.p.) - saline, 3) D-CYSee (100 mg/kg, i.p.) - saline, 4) D-CYSee (10 mg/kg) - fentanyl, or 5) D-CYSee (100 mg/kg) - fentanyl. Extinction testing was conducted for seven days or until extinction criteria were met. Next Long Evans rats (Male, N = 24) underwent a single 5-minute OFT for anxiety under: 1) saline - saline, 2) saline - fentanyl, 3) D-CYSee (100 mg/kg, i.p.) - saline, or 4) D-CYSee - fentanyl. We found that 5 ug/kg fentanyl in males and 50 ug/kg in females induced a significant increase in the percent time spent in the paired chamber over saline-treated control rats. 10 mg/kg D-CYSee significantly reduced the percent time spent in the paired chamber compared to fentanyl controls in females, but failed to induce a significant change in males. Pretreatment with 100 mg/kg D-CYSee significantly reduced the percent time in the paired chamber compared to fentanyl controls in both males and females. D-CYSee alone failed to induce a significant CPP compared to control. Further, open field testing revealed that D-CYSee did not produce maladaptive responding and that fentanyl-induced immobility was preserved. Thus, D-CYSee disrupted the acquisition

of fentanyl seeking in a sex and dosage specific manner without altering motoric or analgesic effects of fentanyl suggesting that D-CYSee has a therapeutic potential to reduce addiction vulnerability during prescribed opioid use.

M2. Investigation of the Necessity and Specificity of the dmPFC Cocaine Seeking Ensemble

Shuai Liu, Bailey Sarka, Xiaojie Liu, Qing-song Liu, Christopher Olsen*

Cocaine use disorder is a chronic and relapsing neuropsychiatric disorder characterized by a strong propensity for relapse upon re-exposure to a previously cocaine-associated environment. The dorsal medial prefrontal cortex (dmPFC) is a critical node in the mesocorticolimbic system related to cue-induced cocaine craving and seeking. There is evidence that learned associations between cues and drug seeking behavior are encoded by specific ensemble of neurons sparsely scattered throughout the dmPFC. Thus, we explored the necessity and specificity of the cocaine seeking ensemble in the dmPFC and hypothesized that inhibition of dmPFC cocaine seeking ensembles inhibits cocaine seeking memory retrieval, and these ensembles are not involved in recall of conditioned fear which is also mediated by the dmPFC. We tested this hypothesis by co-injection of viruses expressing TRE-Cre and a cre-dependent inhibitory PSAM-GlyR into the dmPFC of male and female mice to enable “tagging” of ensemble neurons with an inhibitory chemogenetic receptor. After stereotaxic and jugular catheterization surgery, mice were trained to self-administer cocaine (0.5 mg/kg) for 14 days. After 7 days forced abstinence, a 2-hour drug seeking session was performed and the ensemble was tagged. After another 14 days abstinence, mice received ligand (uPSEM792s) 30 minutes before the second drug seeking session for activation of the chemogenetic receptors. 3 days after the second seeking session, mice received tone-shock associative learning in the fear conditioning training, and a context test and cued test were performed 24 hours after the training. The uPSEM792s ligand was also given 30 minutes before each test. We compared these two seeking sessions and found that chemogenetic inhibition of the dmPFC cocaine seeking ensemble suppressed cocaine seeking. We also quantified the freezing effects during the fear conditioning tests and found that suppression of the cocaine seeking ensemble did not affect fear memory retrieval. These results indicated that the dmPFC cocaine seeking ensemble is necessary for context- and cue-induced seeking memory retrieval, but these ensemble neurons are only specific to cocaine seeking, no effect on fear conditioning memory retrieval.

M3. Investigating the Neurobiological Mechanisms Underlying the Conditioned Reinforcing Effects of Cocaine

Lauren Rysztak, Youngsoo Kim, Robert Kennedy, Emily Jutkiewicz*

One contributor to relapse is the ability of environmental cues that have been associated with drug-taking behavior to evoke drug-craving and -seeking behaviors. Dopamine is thought to play an important role in the primary and conditioned reinforcing properties of drugs, therefore, the current study evaluated dopamine levels in the nucleus accumbens (NAc) during the New Response Acquisition procedure, a stringent test of conditioned reinforcement. This procedure begins with Pavlovian Conditioning in which subjects receive five infusions of cocaine (320 ug/kg/inf) and either simultaneous (Paired) or separate (Unpaired) presentations of a light+tone stimulus per day for 10 days. Then, novel operant manipulanda are introduced into the chamber, and responses produce presentations of cues formerly associated with cocaine (Acquisition). Dopamine levels in the NAc shell during the third day of Acquisition were collected via microdialysis in 10-minute bins throughout the Acquisition session and analyzed by HPLC. Consistent with previous findings, subjects in the Paired group make more active responses than inactive responses for cue presentations than Unpaired subjects. There are no significant group differences in the levels of dopamine between Paired and Unpaired subjects in the NAc shell. We manipulated dopamine levels by local infusion of cocaine (7 or 46 ug) or by systemic administration (10 or 18 mg/kg ip), which failed to alter responding in either Paired and Unpaired groups. Systemic administration of drugs that act on opioidergic (delta opioid receptor agonist SNC80; 3.2 mg/kg sc) or cholinergic systems (muscarinic receptor antagonist scopolamine; 0.32 mg/kg sc), however, can potentiate cocaine conditioned reinforcement. These data suggest that increasing dopamine levels does not drive responding for cocaine paired cues. Future studies will probe other neurotransmitter systems and circuits in mediating the conditioned reinforcing properties of cocaine paired cues.

M4. Ethanol Potentiates Fentanyl-Induced Respiratory Depression

Emma Frye, Renata Marchette, Lyndsay Hastings, Janaina Vendruscolo, Aidan Hampson, Nora Volkow, Leandro Vendruscolo, George Koob*

Drug overdose deaths involving opioids now top 100,000 persons annually in the United States. Opioid overdose deaths primarily occur by respiratory depression, where opioids inhibit both peripheral and central areas responsible for maintaining respiratory rhythm and flow. Alcohol misuse is frequently reported in deaths involving opioids, with estimates of co-involvement of around 30%. While naloxone is effective for reversing opioid-induced overdoses, its efficacy may be lower for co-occurring alcohol-opioid overdoses. This study aimed to characterize the effects of concomitant administration of fentanyl and ethanol on respiratory depression. Male and female Long Evans rats underwent intravenous (i.v.) catheter surgery and were then habituated to the plethysmography chambers. Using whole body plethysmography, we analyzed ventilation parameters on a breath-by-breath basis. The rats were tested in a within-subjects, Latin-square design with four tests one week apart. In each session, rats received 5 mL/kg, i.v. of sterile water, fentanyl (25 g/kg), ethanol (1.18 g/kg), or a combination of fentanyl and ethanol over 1 min. Only the combination resulted in mortality (37.5%), and naloxone administration did not rescue them. Fentanyl, ethanol, and the combination reduced minute ventilation, breathing frequency, peak inspiratory flow, and increased inspiratory time and apneic pauses. The combination more pronouncedly reduced minute ventilation than fentanyl alone and increased apneic pauses than either drug alone. Further investigations will explore what drives the combination's amplification of apneic pauses and other mechanisms of drug interactions that make their concomitant use lethal in animal models. This research contributes to the neurobiological understanding of simultaneous substance misuse, which will be valuable to future investigations that seek effective alternatives and complementary approaches to reverse respiratory depression and prevent overdose deaths.

M5. Sex-Dependent Effects of Alcohol and Oxycodone Polysubstance Use

Yueyi Chen, Salvador Resendiz, Amanda Roberts, Adam Kimbrough*

People use multiple drugs concurrently to self-medicate withdrawal symptoms in the real world. However, preclinical models of concurrent

polysubstance use disorder (PUD), especially alcohol and oxycodone, have not been adequately explored. In this study, we designed two novel preclinical models to explore concurrent alcohol and oxycodone PUD. We hypothesized that withdrawal from one drug would increase the intake of the other. First, we examined the effect of alcohol withdrawal on oxycodone self-administration. Male and female mice received several weeks of chronic intermittent ethanol vapor to become alcohol dependent, while a control group remained alcohol naïve. Mice from both groups self-administered oxycodone intravenously for 2 weeks (during withdrawal from alcohol in the alcohol-dependent group). We found a significant increase in self-administration of oxycodone during the last three self-administration sessions in the male alcohol-dependent mice compared to control mice, suggesting an effect of alcohol withdrawal on oxycodone intake. However, female alcohol-dependent mice did not show the same increase.
Next, we examined the effect of oxycodone withdrawal on alcohol drinking by making male and female mice oxycodone-dependent via i.p. injection every other week. A control group was injected with saline. In between injection weeks during oxycodone withdrawal, mice were given 2-hour 2-bottle choice drinking sessions with alcohol and water. Female oxycodone-dependent mice showed a significant increase in alcohol intake compared to control mice during oxycodone withdrawal. Male mice did not show an effect of oxycodone withdrawal on alcohol drinking. When tested for thermal pain sensitivity, female oxycodone-dependent mice showed a significantly faster latency to withdraw their tails than control mice, while males did not show the same effect. These data suggest an impact of oxycodone withdrawal on alcohol intake.
Together, these data establish models of concurrent alcohol and oxycodone use in mice. We found opposing sex-dependent effects of the drug being used and the drug associated with withdrawal. Males appear more sensitive to the modulation of oxycodone intake by alcohol withdrawal, whereas female mice may be more sensitive to the modulation of alcohol intake by oxycodone withdrawal.

M6. Morphine Exposure and Withdrawal Alters Sleep Patterns in Male and Female Mice

Madigan Bedard, Julia Sparks Lord, Adonay Teklezghi, Isabel Bravo, Lisa Tarantino, Graham Diering, Zoe McElligott*

The opioid epidemic has increased dramatically over the last few decades

resulting in many suffering from opioid use disorder (OUD). The prevalence of opioids and opioid overdose has been driven by the development of new synthetic opioids, increased availability of prescription opioids, and more recently, the COVID-19 pandemic. As we see increases in exposure to opioids, the United States has also seen increases in the frequency of Narcan (naloxone) administration as a life-saving measure for respiratory depression, and, thus, consequently, naloxone-precipitated withdrawal. Sleep dysregulation is one of the main symptoms of OUD and opioid withdrawal syndrome, and therefore should be a key facet of animal models of OUD. We examined the effect of precipitated and spontaneous morphine withdrawal on sleep behaviors in C57BL/6J. We found that morphine administration and withdrawal dysregulates sleep, however not equally across morphine exposure paradigms and not qualitatively the same across sexes. Morphine also increases sleep bout length compared to saline. Given the overlap of brain regions implicated in withdrawal and sleep behaviors, we are investigating physiological changes to these regions using whole-cell electrophysiology as well as therapeutics that might aid in treating both sleep disruptions and withdrawal symptom severity. We have found that oxytocin prevents the withdrawal associated weight loss and has potential for helping sleep dysregulation due to the presence of oxytocin receptors in relevant brain regions. Furthermore, many environmental triggers promote relapse to drug-seeking/taking behavior, and the stress of disrupted sleep may fall into that category. We find that sleep deprivation further dysregulates sleep in mice that had previous opioid withdrawal experience. These findings highlight the importance of understanding and treating withdrawal as naloxone treatments become more common in the face of increasing overdoses.

M7. Impact of Ketamine on Cue-Induced Reinstatement of Cocaine Self-Administration in Rats

Angela Gonzalez, Barbara Sorg*

Strong drug-associated memories are difficult to disrupt. The medial prefrontal cortex (mPFC) is involved in the reconsolidation of cocaine-associated memories. Recent work has shown that presentation of novel information during memory retrieval may render a drug-associated memory vulnerable to disruption in the presence of amnestic agents. Unpublished data from our lab showed that novel memory retrieval in combination with enzymatic disruption of perineuronal nets (PNNS) in

the mPFC reduced cue-induced reinstatement in cocaine self-administering rats. Ketamine has been shown to disrupt drug-associated memories and PNNs. We hypothesized that ketamine would reduce cocaine reinstatement if given during a novel memory retrieval session. Rats were trained to self-administer cocaine on a fixed-ratio 1 (FR1) schedule and given a cocaine-reinforced 30 min memory retrieval session on either an FR1 or novel variable-ratio 5 (VR5) schedule or given no retrieval session. Saline (control) or ketamine (6 mg/kg, i.p.) was administered 10 min pre- retrieval. In a second experiment, control, or ketamine (20 or 50 mg/kg, i.p.) was administered immediately after a VR5 retrieval. In both experiments, the following day, rats were subjected to 30 min of extinction followed immediately by 30 min cue reinstatement. In the first experiment, there was a weak trend toward a reduction of cue-induced reinstatement compared to saline treatment. In the second experiment, there was a trend ($p < 0.07$) at reducing cue-induced reinstatement with a 20mg/kg dose, but no change with the higher, 50mg/kg dose. This suggests that administering a higher dose might promote the expression of the original memory, and that ketamine has potential, but might require different temporal parameters in which it successfully reduces drug-seeking behavior.

M8. Maintenance of Synaptic Function at the Drosophila Neuromuscular Junction is Regulated by Alpha-Ketoglutarate Availability

Jill Farnsworth, Megumi Mori, Mario Calderon, Prasanna Ashok Kumaar, and Pejmun Haghighi*

While life expectancy has more than doubled for humans over the last two centuries, the onset of most age-related health problems remains unchanged. α-ketoglutarate, an intermediate in the Krebs cycle, has garnered much interest in the aging field due to its effectiveness in increasing both the health and lifespan in several animal models. However, precisely how α-ketoglutarate acts to improve health and lifespan remains elusive. We begin to uncover one of α-ketoglutarate's pleiotropic actions by electrophysiological and metabolic investigation and show that maintenance of synaptic function at the neuromuscular junction is regulated by α-ketoglutarate availability.

M9. The Contributions of Neuronal Nitric Oxide Synthase (nNOS) to Cued-Cocaine Seeking

Adam Denton, Ashley Brock, Annaka Westphal, Jayda Carroll-Deaton, Michael Scofield*

Cocaine abuse is a major health concern resulting in ~20,000 cases of overdose each year. Nitrergic interneurons in the nucleus accumbens (NAc) expressing nNOS have been demonstrated to be required for cued-cocaine seeking via the release of nitric oxide. In the present set of experiments we employ small hairpin RNA's (shRNA) alongside transgenic (Tg) mice and rats to further examine the contributions of nitrergic interneurons and nNOS during cocaine conditioned place preference (CPP) and self-administration (SA). In experiment A, Nos1-CreERT2 Tg mice and an mGluR5 shRNA vector were employed to demonstrate that loss of mGluR5, particularly on nitrergic interneurons in the NAc suppresses the expression of cocaine CPP. In experiment B, D1/D2 Cre+ Tg rats and an nNOS shRNA construct were employed to demonstrate that loss of nNOS in the NAc inhibits cued-cocaine seeking following SA and extinction. Morphometric analyses were then employed to examine changes in dendritic spine head diameter (dH) and density following cued-cocaine seeking. We show an increase in dH following cocaine SA compared to saline controls, and a D1/D2 effect for spine density, with D2 rats demonstrating increased spine density, independent of drug treatment or viral manipulation. Our analyses revealed interaction effects for genotype/sex for both dH and density, with D1 females showing an ncreased dH but decreased density coupled with an increase in density for D2 females. Finally, a sex/drug treatment interaction was found for spine density, with cocaine treated males showing the greatest increase in density. Although a marginal interaction effect was present for viral treatment and sex, the effect fell short of statistical significance. While these findings highlight the centrality of nNOS for the behavioral phenomena associated with cocaine reward, they suggest the necessity of further examination of the mechanisms underlying these phenomena, particularly with respect to biological sex.

M10. Mutant Mice Expressing an Internalization-Resistant Form of CB1R Display Altered Cannabinoid Response and Tolerance

*Angela Redmond, Melissa McHann, Mary Piscura, Malabika Maulik, Courtney Lulek, Kayla DeSchepper, Josee Guindon, Daniel Morgan**

Although cannabinoids such as delta-9-tetrahydrocannabinol (Δ9-THC) exhibit clinical efficacy in pain, tolerance to the antinociceptive effects develops with repeated treatment. The focus of our work is to investigate the mechanisms responsible for the acute response and tolerance to different cannabinoid agonists. We previously found that tolerance to cannabinoids is reduced in S426A/S430A mutant mice expressing a desensitization-resistant form of cannabinoid receptor 1 (CB1R) that disrupts the classic mechanism of G protein-coupled receptor kinase (GRK)/βarrestin2-mediated CB1R desensitization. The objective of our current work is to assess the role of CB1R internalization and trafficking on cannabinoid tolerance. This objective will be achieved using a novel six point mutant mouse strain expressing an internalization-resistant form of CB1R that was recently produced in our laboratory. Knock-in mice were produced that express serine/threonine to alanine point mutations for six putative G protein-coupled receptor kinase (GRK) phosphorylation sites in the distal C-terminus of CB1R that are required for the efficient internalization of the receptor in transfected cells. The acute response to CP55,940 and Δ9-THC was assessed by performing cumulative dose response curves. Antinociception was measured using the tail-flick and hotplate tests while cannabinoid-induced hypothermia was assessed by measuring core body temperature. Tolerance to the antinociceptive and hypothermic effects of once daily injections of 0.6 mg/kg CP55,940 was determined. We find a shorter duration for the acute hypothermic effects of CP55,940 and and Δ9-THC in six point mutant mice. Six point mutant mice also display a trend towards enhanced tolerance to the antinociceptive and hypothermic effects of 0.6 mg/kg CP55,940 relative to wild-type littermate controls. This work establishes six point mutant mice as a novel model to study the role of CB1R internalization, trafficking, and resensitization in vivo. Preliminary data shows that cannabinoid tolerance is increased in six point mutant suggesting that the normal processes of internalization, traffickly, and resensitization of CB1R might play an important role in counteracting the development of cannabinoid tolerance.

M11. *POSTER WITHDRAWN*

Synaptojanin-1 Gene Mutations Produce Sex-Specific Changes in Cocaine Reward Through Alterations in Dopamine System Function

Jennifer Mejaes, Jacqueline Saenz, Christopher O'Brien, Carina Pizzano, Samantha Rozario, Pingyue Pan, David Barker*

The synaptojanin-1 (SYNJ1) gene is known to be important for dopamine-related disorders. Mutations of the gene have been linked to bipolar disorder, schizophrenia, and Parkinsonism. Recent evidence has demonstrated that Synj1 deficient mice (Synj1+/-) have impairments in their dopaminergic system, with deficits in several aspects of synaptic vesicular recycling such as endo- and exocytosis. Despite these many links to the dopamine system, little is known about whether Synj1 deficits affect the mesolimbic system, or reward processing. To examine the role of the Synj1 gene in motivated behavior, we subjected male and female Synj1+/- and their littermate controls (Synj1+/+) to a battery of behavioral tests, each designed to capture a unique facet of motivated responding. These tests included a sucrose preference test, operant conditioning, and progressive ratio, as well as a cocaine conditioned place preference paradigm. Overall, we observe that Synj1+/- exhibit a normal behavioral profile compared to controls, with normal hedonic responses and motivated behavior for sucrose. However, male Synj1 +/- demonstrated an attenuated conditioned place preference for cocaine. To further investigate the mechanisms supporting the attenuated response to cocaine, we recorded levels of striatal DA in response to cocaine, levels of the dopamine transporter (DAT) in the midbrain and striatum, and examined how Synj1 deficiencies alter DAT trafficking, in vitro using our novel optical reporter DAT-pHluorin. From these experiments we observed that Synj1 +/- male mice exhibited a weaker DA response to cocaine and failed to show cocaine-induced increases in midbrain or striatal DAT. Our in vitro studies suggest this may be due to a failure in cocaine-induced axonal DAT trafficking.

These findings provide new insights demonstrating that SYNJ1 deficiencies result in abnormal DA system function in males. Additionally, our results also demonstrate a SYNJ-related mechanistic explanation for the strong existence of sex differences, among substance abuse and other dopamine-related disorders.

M12. Social Isolation and Footshock Stress Produce Aggression that is Behaviorally and Biologically Distinct

Michael Conoscenti, Kevin Sattler, Ann Kennedy, Moriel Zelikowsky*

Social interaction is central to mammalian life. Inter-animal aggression represents one of the chief forms of social interaction across species. While aggression is highly adaptive, it can also be deleterious when elicited inappropriately or in excess, as observed following extreme stress. While recent work has begun to elucidate the neural circuit mechanisms underlying aggression, little work has examined the mechanisms of violence produced by stress, and virtually no work has compared the effects of various stressors on aggression. Here, we test the hypothesis that aggression induced by social isolation differs behaviorally and biologically from that induced by footshock. Mice were exposed to three weeks of chronic social isolation stress (SIS) or an acute footshock stressor (FS) and tested for social behaviors using the resident intruder assay. We found that SIS and FS mice approached the intruder from different directions prior to attack and directed aggression towards different parts of the intruder's body. Subsequent analyses using our machine vision action recognition system (MARS) and unsupervised computational approaches were able to decode an animal's condition based off of investigatory behavior prior to attack. These behavioral differences suggest that FS-induced aggression may be mediated by a dissociable biological mechanism from SIS aggression. We hypothesized that the bed nucleus of the stria terminalis (dBNST) may play a selective role in FS- but not SIS-induced aggression, due to its canonical role in anxiety, sensitivity to footshock, and mediating role in an array of social behaviors. To test this, we chemogenetically inhibited dBNST using hM4Di DREADDs and found that FS, but not SIS aggression was reduced. We next employed a combined RNAscope + retrograde tracing approach to genetically identify the population of dBNST cells which are activated following FS-aggression and that send projections to the ventrolateral subdivision of the ventromedial hypothalamus (VMHvl), a region

implicated in the control of mouse aggression. Taken together, our findings suggest that exposure to footshock results in a unique aggression phenotype that may be mediated by unique biological circuits at the intersection of stress and aggression.

M13. OPEN BOARD

M14. Old Brains – New Ideas: A Non-Coding RNA Perspective

Rolf Søkilde, Boye Schnack Nielsen, Erik Kaadt, Lasse Sommer Kristensen, Morten Venø, Dirk Bender, Jørgen Kjems, Betina Elfving*

We have conducted a technical evaluation of long term stored archival FFPE material from the Danish Human Brain Bank. This material has been collected from patients with mental disorders during the period from 1945 to 1982. We have used commercial state-of-the-art in situ probes from ACD Bioscience targeted against microRNAs, to evaluate the quality of the material. Our technical analysis shows that microRNAs are preserved in sufficient quantities and quality to be useful for in situ hybridization against microRNAs. We therefore optimized an automated protocol for the Leica Bond Autostainer, this can then conduct chromogenic ISH stains on 30 slides a day. In the next phase we will evaluate differentially expressed microRNAs from the Human Brain Bank, which have been identified with Nanostring NCounter technology. Three diseases have been selected and carefully curated, Schizophrenia (SZ), Bipolar Disorder (BD), and Depression (DE) with equal representation of male and females. Spatial investigation of the expression patterns of candidate microRNAs will aid the design of functional experiments. This will improve the understanding of the role of microRNAs in these neurological diseases.

M15. Differential Serum and Brain Levels of CACNA1C in Subjects With Bipolar Disorder

*Obie Allen, Brandon Coombes, Mahmoud Eladawi, Rammohan Shukla, Robert McCullumsmith, Barbara Gisabella, Joanna Biernacka, Mark Frye, Matej Markota, Harry Pantazopoulos**

A significant number of patients with bipolar disorder (BD) do not respond to or have difficulties tolerating lithium and/or other mood stabilizing agents. There is a great need for personalized treatments based on biomarkers in guiding psychopharmacologic treatment options.
CACNA1C represents a promising candidate for developing personalized treatments. CACNA1C is one of the most strongly implicated factors in genome-wide association studies of BD. Several lines of evidence suggest that targeting L-type calcium channels is an effective strategy for people with CACNA1C polymorphisms. Polygenic risk factors are enriched in targets of L-type calcium channel blockers. There has been limited investigation of L-type calcium channel blockers verapamil, nimodipine and isradipine as potential mood stabilizers, and evidence in human serum and brain is currently limited.
As a first step in testing the hypothesis that CACNA1C genotype is associated with blood serum levels of CACNA1C, we conducted ELISA measures on serum samples from 100 White subjects with BD from the Mayo Clinic Bipolar Biobank and 100 control subjects from the Mayo Clinic Biobank matched on age, sex, self-reported race, and time of blood draw. We conducted RNAseq on BD and Control brain samples (15/group) to examine gene expression of CACNA1C and additional calcium in the amygdala, given this brain region's role in mood regulation as well as structural and functional abnormalities reported in BD. We observed increased levels of CACNA1C ($p=0.0008$) in serum samples from patients with BD. In contrast, using time of death analysis, we observed a diurnal

variation in gene expression of CACNA1C in the amygdala of subjects with BD, characterized by significantly decreased expression during the day ($p < 0.001$), resulting in enhanced diurnal rhythms in BD.
Our findings represent the first evidence for increased protein levels of CACNA1C in the serum of patients with BD. The contrasting effects in the amygdala vs serum add to the growing literature for brain region differences in CACNA1C expression in people with BD and highlight important differences in peripheral vs brain levels, as well as a key role for altered diurnal expression rhythms. Ongoing analysis will examine relationship of CACNA1C and additional markers with clinical phenotypes and CACNA1C genotypes.

M16. Glucocorticoid Regulation of Striatal Dopamine Transmission

Ashley Holloway, Michael Schaid, Talia Lerner*

Stress is a significant risk factor for the development, and exacerbation, of major depressive disorder (MDD). Corticosterone (cortisol in humans; CORT) is the primary 'stress hormone' in the body. In MDD, normal circadian rhythms of high and low CORT are flattened, leading to dysregulated and chronically elevated levels. Previous studies have found that chronically elevated levels of CORT impair reward-guided operant behaviors but have only reported effects in male mice. After subcutaneous implantation of a slow-release Placebo or CORT pellet, we found that CORT pellet implantation significantly increased circulating levels of CORT in males, but not females. We then found that chronic CORT administration via pellet implantation decreased reward-seeking behaviors in both sexes. CORT treatment also decreased dopamine content of the dorsomedial striatum (DMS) in both sexes. In males, chronic CORT impaired dopamine transporter (DAT) function in the dorsomedial striatum (DMS). Using a DAT inhibitor, we found that chronic CORT treatment blunted the increase in locomotion normally observed after DAT inhibition, but only in males. Using dLight1.3b fluorescence as a proxy for dopamine, we found that DAT inhibition significantly increased dopamine in the DMS of Placebo-treated male mice, but not CORT-treated male mice. DAT inhibition similarly increased dopamine in the DMS of Placebo- and CORT-treated female mice. Using western blot, we found that CORT treatment significantly decreased phosphorylation of DAT in the DMS of male mice, but not female mice. We conclude that CORT treatment impairs reward-seeking in both sexes, and that chronically elevated CORT impairs DAT function in the DMS of male mice.

It remains unclear how CORT affects DAT function in males, and why females are resilient to such an effect. Future studies will address these questions and seek to translate our findings into better diagnoses and treatment options for MDD that take sex differences into account.

M17. Leveraging Analogs of Cardiac HCN -Bradine Drugs to Regulate Dopamine Activity and Achieve Antidepressant Effects

Emily Teichman, Jianping Hu, Xiaoping Hu, Sarah Montgomery, Scott Russo, Carole Morel, Jian Jin, Ming-Hu Han*

Depression is a devastating disease, associated with profound neurophysiological alterations. Upregulation of the hyperpolarization-activated cyclic nucleotide-gated (HCN) channels in ventral tegmental area (VTA) dopamine neurons is associated with depressive-like symptomology in mice. Inhibition of these channels by the HCN inhibitor Cilobradine alleviates those symptoms. Cilobradine is part of the “bradine” family of HCN-inhibiting cardiac drugs which includes Ivabradine, an FDA-approved drug to treat heart disease and heart failure. Here, we aim to augment and refine the HCN-inhibiting, minimally blood brain barrier (BBB)-penetrant features of Cilobradine so as to improve rapid-acting and long-lasting therapeutic effects. 11 analogs of HCN inhibitor Cilobradine and 1 analog of Zatebradine were designed and synthesized. We investigated their effects on VTA dopamine neuron Ih current and firing rate utilizing electrophysiology of brain slices from adult C57Bl6 mice. We also determined the pharmacokinetic profile and brain plasma ratios of the potent analogs. We demonstrated that these different analogs have a variety of inhibitory effects on Ih currents in VTA dopamine neurons. Compounds 10 and 12 were chosen for further study based on their strong inhibition of not only the Ih current but also firing rate; Cilobradine reduced the firing rate of VTA dopamine neurons by 66%, while compounds 10 and 12 led to 91.5% and 92.4% reductions, respectively. Pharmacokinetic analysis determined that the brain plasma ratios of compounds 10 and 12 are 0.28 and 0.57, respectively, greatly improved from the 0.076 brain plasma ratio of parent compound Cilobradine. We demonstrate that minimal changes to the Cilobradine scaffold can alter, and even improve, its inhibitory effect on VTA dopamine neurons. Furthermore, these minimal changes can drastically improve its BBB permeability. Future studies will assess the antidepressant behavioral effects of compounds 10 and 12 in vivo. Our results provide a new avenue of research for the development of novel

therapeutics to alleviate psychiatric disorders associated with dopamine dysfunctions.

M18. Cannabidiol (CBD) as a Treatment for Fragile X Syndrome (FXS) and Autism Spectrum Disorder (ASD)

Ilse Gantois, Junghyun Choi, Laura Marsal Garcia, Nadeem Siddiqui, Nahum Sonenberg*

Introduction: Autism spectrum disorder (ASD) is characterized by symptoms such as reduced social communication and interactions, repetitive behavior and deficits in interests or activities. ASD arises from alterations in brain development that manifests from an early age. ASD is diagnosed in 1 in 160 children worldwide, with an incidence rate that is 4 times higher in males than in females.
Rationale: Recent studies suggest that the endocannabinoid system, a major regulator of behavioral functions in the brain, could be a viable target for FXS and ASD treatment. Cannabidiol (CBD) is a safe and non-mind altering plant based cannabinoid proposed to relieve several psychiatric illnesses including psychosis, addiction, obsessive compulsion, and anxiety related disorders. There is a high interest for CBD's potential for treating FXS and ASD associated symptoms; however, the information on how CBD works in the body, its effectiveness, dosing regime and clinical information remains limited.
Methods and Goal: We are studying the therapeutic effects of CBD for treating symptoms associated with ASD. For the moment we are focusing on mouse models of Fragile X syndrome (FXS), Phelan McDermid Syndrome (PMD) and Neurofibromatosis 1 (NF1), in both males and females. These 3 neurodevelopmental disorders have a high incidence of ASD. We are studying if these mouse models and both sexes respond similarly to CBD treatment at a behavioral level. In addition, since ERK/MAPK and mTOR pathways, involved in controlling protein synthesis, are overactivated in several brain areas of these mouse models, we are studying if CBD administration can correct for this enhanced signaling.
Our work broadens the understanding of the effects of CBD on ASD and potentially supports the implementation of clinical strategies to alleviate symptoms associated with these neurological disorders in both sexes.

M19. Dopamine D2 Receptor Mutations and Hyperkinetic Movement Disorders

Kim Neve, Dayana Rodriguez-Contreras, Joseph Lebowitz, Sheng Gong, Lev Fedorov, Ujwal Shinde, Chris Ford, John Williams*

Two dopamine (DA) D2 receptor mutations were recently found to cause early onset movement disorders with features of chorea and dystonia. One variant found in affected members of a 4-generation Dutch family has the mutation I212F5.61 at the cytoplasmic face of the 5th -helix of the D2 receptor. A second variant found in two unrelated individuals is M374R6.36 at the cytoplasmic face of the 6th -helix. We characterized both variants using BRET assays after expression in HEK293 cells, slice electrophysiology, and computational biology. We have also generated mice carrying the I212F variant, Drd2I212F mice. The density of D2 receptors on HEK293 cell membranes was decreased by ~60% for either pathogenic variant compared to D2-WT after transfection of the same amount of receptor cDNA; a similar reduction in striatal D2 receptor density was detected in homozygous Drd2I212F mice. In BRET assays, both pathogenic variants exhibited moderately decreased binding of arrestin. Constitutive and agonist-stimulated activation of G proteins and G protein-mediated signaling in HEK293 cells was enhanced for both pathogenic variants compared to D2-WT, but considerably more for M374R than for I212F. Molecular dynamics simulations provide a structural rationale for enhanced G protein activation. Following AAV-mediated expression of pathogenic D2 receptor variants in midbrain dopamine neurons of mice lacking endogenous D2 autoreceptors, electrically evoked IPSCs, reflecting somatodendritic DA release, exhibited slow kinetics (e.g., slower decay) compared to D2-WT; kinetics for M374R were much slower than for I212F. Similar slow kinetics were observed in midbrain dopamine neurons and striatum from Drd2I212F mice compared to Drd2+/+ mice. Drd2I212F mice exhibited gait abnormalities resembling those in other mouse models of chorea or dystonia. We anticipate that mouse models will be useful for examining the mechanisms of pathogenicity of these DRD2 variants and for testing therapeutics.

M20. Role of D1- and D2-RECEPTOR Prefrontal-Accumbens Circuits in Cognitive Flexibility and Stress-Related Pathology

Matthew Hearing, Aditii Wakhlu, Ahman Edwards, Eden Anderson*

Deficits in cognitive flexibility is one of the most consistently documented cognitive problems in neuropsychiatric disorders and contributes to reduced emotional control and increased susceptibility to negative life events (e.g., stress). This dynamic behavior requires coordinated activity of pyramidal neurons in the prelimbic region of the medial prefrontal cortex (PrL-PFC) to brain regions such as the mediodorsal thalamus (MDT) and nucleus accumbens core (Core). Within these circuits lie subcircuits comprised of pyramidal neurons that selectively express dopamine type 1 (D1) or type 2 (D2) receptors that differentially contribute to processing of information related to decision-making, however their exact contributions remain unknown. We combined a model of attentional set-shifting to assess cognitive flexibility and a Cre-dependent viral approach in D1- and D2-Cre transgenic mice to promote expression of the inhibitory designer receptor exclusively activated by designer drug (DREADD), hM4Di, or mcherry control in PrL-Core subcircuits (D1-Core, D2-Core). In male mice, intra-PrL infusion of clozapine-n-oxide increased the impaired performance during an extradimensional set-shift test of flexibility in D1-Core but not D2-Core mice compared to controls. Alternatively, performance was not impaired by inhibition of either D1- or D2-Core circuits in females. Follow up studies in males and females targeting the PrL-Core circuit as a whole showed impaired performance in males but not females. Alternatively, inhibiting PrL pyramidal neurons regardless of downstream projection impaired performance in females but not males. These data suggest that D2-Core circuits in males play a larger role in regulating flexible behavior and highlight a previously unobserved sex difference in the neural circuits required for flexibility. Ongoing studies targeting alternate circuits in females and examining a link between circuit dysfunction in stress-mediated impairments in cognitive flexibility and the associated neural adaptations within these sub-circuits.

M21. Stress-Resilient Mice Optimize Subjective Value and Food Security on an Economic Foraging Task

Romain Durand-de Cuttoli, Freddyson J. Martinez-Rivera, Long Li, Angelica Minier Toribio, Scott J. Russo, Eric J. Nestler, Brian M. Sweis*

Economic stress can often serve as a “second-hit” for those who have already accumulated a history of stressful experiences. This can

precipitate significant changes in behavior that may be adaptive or maladaptive depending on one's unique stress-response predispositions. How an individual recovers from a setback is a core feature of resilience but is seldom captured in animal studies. Here, we challenged mice in a novel two-hit stress model by first exposing animals to chronic social defeat stress (first hit) – a protocol known to separate individual differences in stress-resilient versus stress-susceptible phenotypes. Mice were then tested longitudinally across two months on the neuroeconomic task termed "Restaurant Row" during which mice foraged daily for their sole source of food while on a limited time budget. An abrupt transition into a reward-scarce environment on this task elicits an economic crisis (second hit) precipitating a massive drop in food intake that mice must respond to in order to survive. We found that stress-resilient mice mounted the most robust behavioral response to this economic challenge and readily renormalized food intake back to baseline levels faster compared to stress-susceptible and non-defeated control mice. This was achieved through an efficient increase in effort expenditure and a redistribution in how time was allocated among competing opportunities. Interestingly, stress-resilient mice learned to accomplish this while simultaneously maximizing subjective value by re-establishing flavor preferences that approximated yield previously obtained in a reward-rich environment. These findings suggest that a resilient individual's capacity to "bounce back" following economic stress while foraging entails the development of a multi-pronged strategy that not only ensures food security necessary for survival but also prioritizes other aspects of well-being including subjective value, highlighting a motivational balance that may be impaired in depression.
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M22. Stimulation of the Rostromedial Tegmental Nucleus Induces Long-Lasting Avoidance Behavior

Jacob Watson, Peter Vento, Maddy Lopez De Leon*

The activity of midbrain dopamine neurons has long been associated with approach and reinforcement learning, yet it is less clear how inhibition of dopamine signaling contributes to behavioral inhibition and avoidance. The rostromedial tegmental nucleus (RMTg) provides a dense inhibitory projection to dopamine neurons in the ventral tegmental area (VTA). We previously demonstrated that the inactivation of the

RMTg - VTA pathway in rats causes persistent reward-seeking under punishment. To test whether stimulation of this circuit is sufficient to suppress reward-seeking and induce avoidance, we employed an optogenetic approach using timing- and pathway-specific excitation of the RMTg - VTA pathway in two different food-seeking paradigms. In a one-lever operant task in which rats were trained to lever press (FR5) for standard food pellets, we found that brief (30sec) optical stimulation of the RMTg - VTA pathway immediately after completion of the FR significantly reduced the number of reward trials rats completed over a 30min test session, with this behavioral suppression becoming more robust over repeated light-paired sessions. As subjects in this one-lever task were only given the option of whether to “press or suppress”, we next tested a separate group of rats in a two-flavor preference paradigm in which two reward options were available (vanilla or chocolate-flavored pellets). Here, we found that pairing optical RMTg - VTA stimulation with one of the two reward options caused a rapid and robust shift to the opposite (non-paired) flavor, in stark contrast to the general suppression of behavior observed in the previous one-lever task. Notably, rats in the flavor preference paradigm exhibited nearly complete avoidance of the light-paired flavor that persisted for weeks. Together, these data suggest an essential role for the RMTg - VTA pathway in both behavioral inhibition and conditioned avoidance, with differing effects depending on the avoidance strategy subjects employed.

M23. Melanocortin-4 Receptor Control of Striatal-Dependent Action Selection

Elizabeth Heaton, Shannon Gourley*

Goal-directed action refers to behaviors that are dynamic, sensitive to unexpected events, and require the dorsomedial striatum (DMS). Meanwhile, habitual behaviors are reflexive and unchanging and rely on the dorsolateral striatum (DLS). Molecular factors underlying an organism’s ability to flexibly shift between goal-directed and habitual behavior are incompletely understood. We recently discovered that striatal melanocortin-4 receptor (Mc4r) expression correlates with this behavioral flexibility in adult male and female mice. To identify functional consequences, we used viral-mediated gene silencing to reduce Mc4r. Mc4r knockdown in the DMS enhanced the ability of mice to select actions based on reward likelihood and value, while reduction in the DLS

facilitated habit formation. Thus, reducing MC4R enhanced the functions of distinct striatal subregions in decision making. MC4R controls GluA2 AMPA receptor subunit availability at the membrane of medium spiny neurons, leading to the hypothesis that chemogenetic manipulation of Mc4r+ DMS neurons would impact expression of behavioral flexibility. Stimulation of Mc4r+ DMS neurons via Gq-coupled Designer Receptors Exclusively Activated by Designer Drugs (DREADDs) facilitated animals' ability to select actions based on reward likelihood. Meanwhile, inhibition via Gi-DREADDs rendered animals insensitive to changes in reward likelihood, promoting habits. These results reveal that striatal MC4R may be a key factor in sustaining versus "breaking" habits, and thus could serve as a target for treating maladaptive habits that contribute to neuropsychiatric disease.

M24. Calcium Activity is a Degraded Estimate of Spikes

Evan Hart, Matthew Gardner, Marios Panayi, Thorsten Kahnt, Geoffrey Schoenbaum*

Recording action potentials during behavior has led to fundamental discoveries regarding neural function in sensory, memory, motor, and learning systems. These successes have led to the widely accepted notion that extracellular spikes represent key units of neuronal output. Methods have also been developed to measure cellular signals, particularly calcium flux, that can correlate with spiking. While calcium imaging in anatomically or genetically identified cells has extended what could be learned from electrophysiological recording, these studies were typically grounded in prior unit recording work; more recent work has increasingly used calcium as a proxy for neural activity without reference to unit data, even though the spike-to-fluorescence transformation is unpredictable under real-world conditions. While calcium sensors have been validated in-vitro, it is unclear how closely calcium activity hews to the underlying biological signal of interest, action potentials. Thus, drawing conclusions from these data when they are not supported by unit findings – or even contradict them – is fraught. In sensory and motor tasks, calcium and spikes produced different results. While consistent with the conclusions that visual cortex neurons encode visual features and motor cortex neurons signal movement direction, differences raise the question of whether spikes and calcium activity contain the same information during complex cognitive operations. To address this question, we recorded and

imaged the orbitofrontal cortex (OFC) during olfactory discrimination learning, since both have rich, well-studied neural correlates. In a variety of settings, OFC signaled information about reward predictions and the sensory properties of odor cues in humans, nonhuman primates, and rats.

M25. Validation of a Digital Therapeutic to Improve Gait Performance in Parkinson's Disease: The Dual-Task Augmented Reality Treatment (DART) Platform

Anson Rosenfeldt, Ryan Kaya, Amanda Penko, Matthew Streicher, Eric Zimmerman, Benjamin Walter, Jay Alberts*

Background: Automaticity deficits in Parkinson's disease (PD) are exploited under dual-task conditions which underlies postural instability and gait dysfunction (PIGD). Dual-task training (DTT) improves automaticity and gait performance in PD. Delivering DTT is time and cost intensive; the digitization of DTT can expand the availability of an effective intervention to treat PIGD. The Dual-task Augmented Reality Treatment (DART) platform was designed to simultaneously deliver DTT and objectively measure gait and cognitive performance.
Objective: To validate a digital therapeutic for the treatment of PIGD by comparing outcomes from two groups of PD patients randomized DART or traditional DTT. It was hypothesized that the improvements in gait parameters would be equivalent across groups.
Methods: A single-blind randomized controlled trial was completed in which individuals with PD and gait dysfunction were randomized traditional DTT or DART intervention twice a week for eight weeks. Digital versions of DTT activities were developed and delivered to the DART group via the HoloLens2 augmented reality headset. Primary outcomes included clinical symptom measures and biomechanical outcomes characterizing gait under single- and dual-task conditions at baseline and end of treatment.
Results: Forty-seven individuals completed the intervention (traditional DTT = 22, DART = 25) and were included in the analysis. Clinical measures of PD symptoms did not change over the 8-week period. Gait velocity increased under single- and all dual-task conditions from baseline to end of treatment with improvements in several conditions meeting equivalence. Cadence and step length also increased in the majority of the dual-task conditions. Improvements in gait were largely maintained for both groups 8-weeks after EOT.

Conclusions: Equivalent improvement in gait parameters across the DART and DTT groups provides initial validation for the use of the DART platform as a digital therapeutic for improving PIGD associated with PD. This is the first digital therapeutic for PIGD that has undergone rigorous comparison to an existing evidence-based treatment (DTT). The DART platform can increase accessibility for the treatment of PIGD.

M26. Trem2R47H NSS; 5xFAD Mice Display Age/Disease Progression-Dependent Changes in Plaques and Plaque-Associated Microglia, and Increased Plasma Neurofilament Light Chain

Kim Green, Kristine Tran, Shimako Kawauchi, Celia Da Cunda, Narges Rezaie, Heidi Liang, Ali Mortazavi, Andrea Tenner, Frank LaFerla, Grant Macgregor*

Genome-Wide Association Studies revealed Triggering receptor expressed on myeloid cells 2 (TREM2) R47H mutation as one of the strongest genetic risk factors for late-onset Alzheimer's Disease (AD). In the brain, TREM2 is a transmembrane receptor expressed exclusively by myeloid cells. Many current TREM2*R47H mouse models have observed evidence of cryptic splicing products of the mutant allele, resulting in artefactually reduced protein product. Model Organism Development and Evaluation for Late-Onset Alzheimer's Disease (MODEL-AD) consortium at University of California - Irvine has developed the Trem2R47H NSS (Normal Splice Site) mouse model where the Trem2 allele is expressed at a level similar to the wild-type Trem2 allele, with no evidence of cryptic splicing products from the mutant allele. In this experiment, we set out to investigate this mouse model on C57BL/6J background and the effect the variant has on AD pathology when crossed with 5xFAD mice, generating four groups – WT, Trem2R47H homozygous, 5xFAD, and 5xFAD/ Trem2R47H homozygous.
Analyzing subiculum and cortical confocal images reveals sex-related differences in dense-core Aß plaque burden and size in 4-month 5xFAD/ Trem2R47H, where female 5xFAD/ Trem2R47H mice exhibit increased plaque load compared to 5xFAD mice. In males, stark reductions in plaque load are observed. This sex-difference is not observed at 12-month. Examination of IBA1+ microglia at 4-month reveals significant reductions in microglia volume in both Trem2R47H and 5xFAD/ Trem2R47H mice compared to their controls. Notably, there is a significant impairment of plaque-microglia interaction in 5xFAD/ Trem2R47H at 4-month that is rescued at 12-month. Moreover, we find a

significant increase in plaque-associated neuritic damage in 5xFAD/ Trem2R47H when immunolabeled with LAMP1 at 4-month that was also absent at 12-month. Similarly, plasma neurofilament light chain levels revealed significant increases in brain damage of 5xFAD/ Trem2R47H compared to 5xFAD at 4-month and a trending increase at 12-month. Collectively, these results show the effects of the Trem2R47H variant on plaque development and downstream pathology, highlighting sex differences as well as age/ disease progression-dependent changes.

M27. Oxytocin Can Help Prevent Opioid-Induced Respiratory Depression

*Olga Dergacheva, Joan Escobar, Caitlin Ribeiro, Emily Cheung, David Mendelowitz**

Opioid overdose kills 130 people in the US every day in large part due to opioid-induced respiratory depression (OIRD). Opioids suppress respiratory drive, respiratory rate, tidal volume and chest wall compliance, as well as increase upper airway resistance. Fortunately, mu opioid receptor (MOR) antagonists, such as naloxone, are highly effective in reversing OIRD. However, MOR antagonists also reverse analgesia which often limits their use and can precipitate acute withdrawal symptoms. The identification and validation of new therapeutic agents to counteract life-threatening OIRD is desperately needed. Our works tested if oxytocin may fulfill these criteria and serve as a novel prevention and treatment for OIRD by facilitating central control of breathing and reducing upper airway obstructions to improve respiratory function compromised by opioids. Oxytocin administered in rats at a concentration of 100 nmol/kg IP, simultaneously with fentanyl (IP, 0.2 mg/kg), significantly ($p<0.05$) inhibited OIRD and increased minute ventilation (54.6%), breathing frequency (32.1%), tidal volume (17.9%), peak inspiratory flow (54.2%) and peak expiratory flow (42.3%) compared to untreated fentanyl administration. To test if oxytocin can reverse OIRD that has already reached the nadir of impaired respiratory function we conducted a second series of experiments in which a higher dose of fentanyl (IP, 0.5 mg/kg) was administered and OIRD was allowed to reach a steady state depression for 10 minutes before oxytocin treatment was administered (200 nmol/kg IP). Oxytocin treatment (200 nmol/kg IP) administered 10 minutes after OIRD was established with fentanyl, significantly improved respiratory frequency ($p=0.003$), minute ventilation ($p=0.003$), peak inspiratory flow ($p=0.02$) and peak expiratory

flow (p=0.01) in animals when compared to untreated animals. In conclusion, our preliminary results indicate oxytocin could help reverse OIRD.

M28. Caveolae-Mediated Spontaneous Transient Vasospasm After Ischemic Stroke

Luis Tovar-y-Romo, Ricardo Santana-Martínez, Alfredo Cárdenas-Rivera, Juan Manuel Tzompantzi*

Rapid recanalization following an acute ischemic stroke can minimize brain infarct growth and recover the better part of the salvageable penumbral tissue in the brain. Therapeutic interventions are limited to specific clinical statuses and by the elapsed time after the initial symptoms. We observed a random non-reperfusion phenomenon caused by vasospasm in a preclinical model of ischemia/reperfusion in the rat by occluding the middle cerebral artery. Thus, we decided to investigate the mechanisms underlying the initiation of reperfusion. We monitored the reperfusion phase after the stroke using laser Doppler flowmetry over the cortical territory irrigated by the middle cerebral artery in the rat. We determined that some of the experimental subjects presented a phenomenon of delayed reperfusion and had an increased, more extensive infarction. In vivo two-photon microscopy in the mouse established that this effect was due to vasospasm. We evaluated several mechanisms of vasoconstriction, namely, the activation of L-type voltage-dependent calcium channels, synthesis of 20-HETE, activation of piezo channels, and caveolae physiology, and determined that the transient vasospasm correlated mainly with caveolae function. This study provides mechanistic information about the physiological circumstances that prevail immediately after reperfusion and points to the immediate regulation of caveolae activity to reduce brain damage.

M29. Locus Coeruleus-Noradrenergic System Impairment After Repeated Mild Traumatic Brain Injury

*Leah Horvat, Alexis Foschini, Doug Fox, Barry Waterhouse, James Grininas, David Devilbiss**

Mild traumatic brain injury (mTBI) is a critical health and economic issue for approximately 3 million Americans each year. Mild TBI is a complex pathophysiological process resulting in behavioral and cognitive deficits including impaired arousal, attention, decision-making, and other

executive functions. Although symptoms generally resolve quickly after a single insult, 1 in 5 patients with mTBI exhibit symptoms for more than a month. Persistent cognitive deficits are central to patient difficulties returning to work and activities affecting quality-of-life. Moreover, repeated mTBI can produce more severe, longer-lasting cognitive impairments and brain damage than single injuries and can result in outcomes similar to severe TBI. Catecholamine systems, including the locus coeruleus (LC) -norepinephrine (NE) pathway, are critical regulators of the higher executive processes affected by TBI. Impaired LC-NE function is implicated in the pathogenesis of the cognitive and neuropsychiatric symptoms following moderate to severe TBI. However, the effects of mild TBI and repetitive TBI on LC-NE function are poorly understood. Psychostimulants, including methylphenidate (MPH), act as catecholamine reputake blockers to increase NE and other catecholamines and are used to improve arousal and executive processes following TBI. However, the variability in efficacy of MPH therapy across the TBI patient population is poorly understood.
We posit that altered catecholamine system function likely underlies the behavioral and cognitive deficits found after mTBI and variable responsivity to this class of drugs. We found a reduction in dopamine-β-hydroxylase (DBH) immunoreactivity within the prefrontal regions of the rat brain following repetitive mild TBI. Additionally, baseline LC neuron discharge patterns, NE efflux within the prefrontal cortex, and the response of the LC-NE system to the MPH challenge were significantly altered after repetitive mild TBI. These findings provide critical insight into the sensitivity of catecholamine fibers to repeated mild TBI and support for the role of noradrenergic fiber injury in the cognitive deficits resulting from repeated injury.

M30. The Lateral Preoptic Area Controls the Effects of Social Isolation on Mouse Courtship Behavior and Song

Erin Carroll, Jay Love, PhD, Michael Conoscenti, Ashley Covington, Moriel Zelikowsky*

Social communication is a vital component of courtship behavior across species. Through a series of behavioral experiments and acoustic recordings, we have discovered that chronic social isolation (SI) significantly alters mouse mating behavior and associated ultrasonic vocalizations (USVs). Detailed analysis of audio recordings collected from male mice during a homecage mating assay with a female

conspecific reveal significant differences in USV production patterns, where isolated mice produce longer song syllables at a lower frequency with a smaller frequency range and fewer frequency jumps than group housed males. Importantly, we found that isolation negatively impacted behavioral chains of events such that Markovian principles were followed in group housed mice but were not present in isolated mice. Moreover, we found a strong correlation between female defensive behaviors and male mating attempts for group housed mice, but this relationship was not present for isolated mice, suggesting that isolation disrupts the relationship between male mounting behavior and female receptivity. This was supported by follow-up experiments demonstrating that females preferred interacting with group housed males vs. isolated males in a modified 3-chamber social interaction assay. We complemented these behavioral and acoustic approaches with neural circuit analyses. Isolated males with altered USVs showed increased cfos expression in the lateral preoptic nucleus (LPO), a region previously implicated in mouse USVs more generally. To further probe the role of the LPO in SI- mouse song, mice were injected with fluorescently encoded calcium indicators and implanted with GRIN lenses to assess the in vivo activity of neurons in the LPO during mating behavior and USVs. Initial results revealed correlated activity of neurons in the LPO during SI-mouse USVs. Collectively, our findings indicate that SI negatively modulates mouse courtship behaviors and song, and that this modulation is encoded by unique ensembles of neurons in the LPO.

M31. Designer Molecules of the Synaptic Organizer MDGA1 Reveal 3D Conformational Control of Biological Function

Gabrielle Rudenko, Hubert Lee, Nicolas Chofflet, Jianfang Liu, Shanghua Fan, Mischa Machius, Gang Ren, Hideto Takahashi*

Synaptic adhesion and organizing molecules, also known as ‘synaptic organizers’, play an essential role in promoting synapse development. The synaptic organizers neuroligins (NLGNs) and neurexins (NRXNs) protrude into the synaptic cleft where they form trans-synaptic macromolecular bridges with each other specifying synaptic function. The cell surface molecules MDGA1 and MDGA2 (MAM domain-containing glycosylphosphatidylinositol anchor) block NRXN:NLGN trans-synaptic bridges by shielding NLGNs from NRXN binding, impacting the development of inhibitory versus excitatory synapses, respectively. Alterations to this trio of proteins (MDGAs, NRXNs, and NLGNs) are

thought to lead to an imbalance in excitation versus inhibition disrupting neural circuits critical for cognition and behavior. Indeed, MDGAs, NLGNs, and NRXNs are implicated in many neuropsychiatric disorders including autism spectrum disorder and schizophrenia.
The large, multi-domain extracellular region of MDGA1 adopts a striking triangular shape, alone and in complex with NLGNs, in crystal structures. Whether this unusual arrangement is required for biological function and binding to NLGNs is unknown. Here, we show that MDGA1 adopts compact but also extended 3D conformations. Designer mutants targeting strategic molecular elbows in MDGA1 alter the distribution of 3D conformations while leaving the binding affinity between soluble ectodomains of MDGA1 and NLGN2 essentially intact. However, these designer mutants trigger unique functional consequences, despite the mutations being located far from the MDGA1:NLGN2 interaction site. Our data suggest that the 3D conformation of the MDGA1 ectodomain is critical for its function, and that its NLGN binding site located on the Ig1-Ig2 domains is not independent from the rest of the molecule. Furthermore, conformational changes to the MDGA1 ectodomain via strategic hinges may form a molecular mechanism to regulate MDGA1 action within the synaptic cleft.

M32. The Psychedelic 5-HT2A/2C Agonist DOI Influences Nucleus Accumbens Dopamine Signaling During Reward Prediction

David Martin, Angel Delgado, Donna Calu*

Psychedelic drugs like LSD and psilocybin are 5-HT2A agonists that alter cognition, such as the processing of sensory information, and have been suggested to influence predictive encoding more generally. Dopamine signaling in the nucleus accumbens is a component of reward prediction and reward value processing. In rats, we determined that the 5-HT2A/2C agonist, DOI, produces acute changes in the value of rewards. We hypothesized that DOI would alter dopaminergic signaling associated with both reward prediction and reward value. Here, we conducted experiments to determine the effects of DOI on pavlovian and instrumental behaviors motivated by different rewards (food and water) and their associated cues. To determine the effects of 5-HT2A agonism in a critical reinforcement learning pathway, we optically measured dopamine signaling in the nucleus accumbens through virally transfected GRAB-DA receptors during reward-motivated behaviors. Our results suggest that 5-HT2A receptor agonism decreases operant

motivation for caloric rewards (food and sucrose) at all price points but increases motivation for water at low price points. In pavlovian tasks, we observed no DOI-induced changes in dopaminergic transient peaks to unpredicted (distal) cues signaling upcoming water delivery, but observed decreases in transients to cues signaling upcoming food delivery. Interestingly, in tasks where both a distal (early) cue and a subsequent proximal cue predict reward delivery, 5-HT2A stimulation increases the relative size of the proximal or predictable cue, relative to the distal or unpredictable cue. Such dopamine signaling patterns resemble dopamine transients in early pavlovian learning before late cues are fully predicted. Overall, our results are consistent with DOI altering dopaminergic signaling through reward-dependent changes in value as well as through reward-independent effects, potentially involving increased prediction uncertainty.

M33. G-Protein Coupled Receptor Activation Based (GRAB) Photometery Reveals Serotonin Release During Reward Consumption in the Dorsal Striatum

Mitchell Spring, Katherine Nautiyal*

In the Dorsal Striatum (DS), pharmacological manipulation of the serotonin system disrupts behavioral control and the prospective encoding of rewards. However, the precise role of serotonin signaling in the dorsal striatum during reward related behavior has been difficult to determine. This difficulty is due, in part, to a lack of available techniques suitable for measuring serotonin release on a timescale compatible with single reward trials. Recent advances in G-protein coupled Receptor Activation Based (GRAB) fluorescent proteins enable monitoring such dynamics in real time. Seeking to parse the involvement of serotonin in striatal reward processing, I monitored serotonin levels using GRAB-5-HT in the DS of male and female adult mice during reward presentations of different concentrations of evaporated milk. Following an initial training period to establish consumption, fluorescent activity was recorded through a fiber optic implanted in the DS at the site of viral expression of GRAB-5HT. Serotonin release was quantified by identifying serotonin transients (i.e. brief periods of increased activity) according to threshold criteria and measuring their alignment to behavior. During access to 100% evaporated milk, 83% of transients occurred during licking, with 96% of licks occurring within 2 seconds of the onset of a transient. In

sessions, mice were provided alternating access to a low (20%) and a high (100%) concentration of milk and also access to six concentrations of milk (0-100%). Behaviorally, higher concentrations elicited more consumption. Transient frequency (in events/second) was unaffected by concentration, while both transient magnitude and duration tended to increase with milk concentration. The association of striatal serotonin signaling with licking behavior suggests that it is involved in some aspect of anticipation, motivation, or approach. Ongoing studies are focused on disentangling these processes from value encoding and motor output.

M34. Barriers to Entrepreneurship for Women Neuroscientists

Bradley Tanner, Mary Metcalf*

NIH's invested $42.9 billion in 2021 and funded 56,794 research grants. Translating that activity and the revolutionary changes in the field of brain research requires entrepreneurial activity by life scientists. Although women receive the majority of science PhDs and hold 47% of the research positions, they head only 12% of biostartups. In healthcare, women and women of color represent 67% and 22% of entry-level jobs. Yet in the c-suite, the comparable numbers are 29%/5% for women/women of color.

To address perceived and actual barriers to entrepreneurship for women we completed an exhaustive literature review and involved 31 women at all stages of life sciences careers in needs analysis and solution design. 71% identified low confidence in entrepreneurial ability as a significant barrier. Lack of role models and doubt about their business communication skills were common. Women in life sciences would benefit from an intervention that builds entrepreneurial self-efficacy and, if desired, entrepreneurial intent.

We engaged consultants and women in life sciences including entrepreneurs. Focus groups helped define a unique strategy to complement standard approaches such as informational resources, MBA training, and startup incubators. Since, mentorship fuels entrepreneurial intent and confidence, women wanted examples and guidance, especially from other women. Their top interest included fictional narratives highlighting women's successes in life science firms and real-life examples of successful mentorship and entrepreneurship. They identified stories in the 3rd person, 1st person interviews, and example focus groups – each followed by key points, tips, and take-home

messages. Secondly, to enhance barrier-breaking skills development they wanted an interactive branching path narrative with decision points and customized immediate feedback. Finally, they wanted to assess their readiness for business in terms of their intent and self-efficacy in the form of “Are you ready?” interactive quizzes.
Current work is testing the impact of linear narratives on established scales of entrepreneurial intent and self-efficacy, customized for an audience of life scientists and its unique challenges. Results are guiding interactive dialog elements including branching path experience and self-query tools.

M35. Exposure to SNC-80 or Persistent Pain Alters Delta Opioid Receptor Signaling in Anterior Cingulate Cortex Parvalbumin Neurons

Marie Walicki, Alberto Perez-Medina, William Birdsong*

The anterior cingulate cortex (ACC) plays a role in the neural circuitry of pain and its output influences downstream neural circuits. ACC hyperexcitability is shown in chronic pain conditions, and direct inhibition of ACC activity provides relief from pain. ACC activity is regulated by endogenous opioids like enkephalins, which can act at both mu and delta opioid receptors to alter cortical function. The delta opioid receptor (DOR) is expressed in a majority of parvalbumin (PV) interneurons within the ACC and DOR activation on these interneurons inhibits GABA release, disinhibiting nearby pyramidal cells. DOR activation has multiple cellular effects activating a potassium conductance at PV cell soma and inhibiting neurotransmitter release from presynaptic axon terminals. DOR signaling in some brain regions can be dynamic, changing in response to repeated drug exposure or chronic pain. Within PV cells in the cortex, it is not known whether DOR signaling adapts to drug exposure or pain and whether DOR signaling in soma and presynaptic terminals is differentially regulated. The aim of this study was to understand DOR signaling adaptations in soma and presynaptic terminals in response to repeated drug exposure and pain. We used patch clamp electrophysiology, optogenetics and pharmacology in brain slices to measure somatic and presynaptic DOR signaling following repeated exposure of mice to the selective DOR agonist SNC-80. SNC-80 treatment induced cross tolerance to Met-enkephalin in both somatic and presynaptic effector pathways, however tolerance at the soma developed more rapidly. Additionally, exposure to SNC-80 altered DOR regulation of feed-forward inhibition in the ACC. Like SNC-80

treatment, persistent pain resulted in tolerance to Met-enkephalin at the presynaptic effector pathway. Pretreatment with naloxone, an opioid antagonist prior to pain reversed this tolerance effect. These data suggest that development of cellular tolerance in ACC PV neurons is heterogenous based on subcellular receptor location and that SNC-80 treatment and pain can disrupt endogenous opioid signaling.

M36. Characterization of a Nociceptive Amygdala to Accumbens Neural Circuit

Jessica Wojick, Nora McCall, Justin James, Gregory Corder, Susumu Tonegawa*

Why does the experience of pain hurt, feel unpleasant, and lead to protective behaviors? A key first step to understand pain aversion is to functionally and genetically identify nociceptive neurons connected across affective-motivational neural circuits and to understand how acute and chronic pain affects these circuits. We recently identified a nociceptive subpopulation of negative valence basolateral amygdala (BLA) neurons essential for pain aversion (nociBLA). We used targeted recombination in active populations (TRAP) mice to genetically capture nociBLA neurons and to test their necessity and sufficiency to produce nociceptive hypersensitivity and negative affective behaviors. Next, we imaged bulk fluorescent calcium activity of negative valence Rspo2+ BLA somas and axon terminals in a downstream target of nociBLA neurons—the nucleus accumbens Shell (NAcSh)—across the transition from acute to chronic neuropathic pain. Broadly, aberrant activity of the NAcSh has been linked to motivational deficits in chronic pain, yet much remains unknown regarding specific NAcSh nociceptive cell-types or their modulation by nociBLA neurons. We found Rspo2+ BLA axon terminals are inhibited in response to salient noxious and non-noxious stimuli. Using histological methods, we found a previously unreported nociception-active posterior medial NAcSh subnuclei, which we termed the “NAcre,” that receives projections from nociBLA neurons. Importantly, the majority of acute NAcre neurons also display increased FOS expression to light touch after a peripheral nerve injury, revealing consistent activation across pain states. Finally, we found NAcre neurons primarily expressed dopamine receptor 2 and kappa opioid receptor mRNA. In total, the NAcre is a nociceptive subregion of the NAcSh that receives transmissions from the BLA. Further work will determine the necessity and sufficiency of this BLA to NAcre circuit for affective-motivational behaviors in acute and chronic pain states.

M37. Combined Analysis of Caudate and DLPFC Transcriptomes Defines Two Molecular Subtypes of Schizophrenia

C. Harker Rhodes, Eva P. Childers, Elijah F. W. Bowen, Richard Granger*

the cocaine seeking ensemble did not affect fear memory retrieval. These results indicated that the dmPFC cocaine seeking ensemble is necessary for context- and cue-induced seeking memory retrieval, but these ensemble neurons are only specific to cocaine seeking, no effect on fear conditioning memory retrieval.

Our previous analysis of expression array data from the DLPFC of a cohort of 189 adult schizophrenics and 206 adult controls identified 633 genes which are differentially expressed at levels of statistical significance which survive Bonferroni correction. To our surprise we observed that that statistical significance was being driven by about half of the schizophrenic patients. In other words, the schizophrenics patients could be divided them into two groups, "type 1" patients who have a DLPFC transcriptome similar to that of controls with no genes differentially expressed at a statistically significant level, and "type 2" schizophrenics who had DLPFC transcriptome dramatically different from that of controls with 3,652 expression array probes to 3,200 genes detecting transcripts that are differentially expressed at a level of statistical significance which survives Bonferroni correction.

In the present study we confirm that result by examining RNAseq data from the DLPFC of a cohort which substantially overlaps the original cohort, ruling out the possibility that our original observation was the result of some unidentified technical limitation of expression arrays. We then extend those results by examining RNAseq data from the caudate of the same subjects and observing that patients identified as “type 1” or “type 2” based on their DLPFC transcriptomes also have caudate transcriptomes which are either very similar to, or very different from the caudate transcriptomes of the control subject

Tuesday, January 24, 2023

POSTER SESSION IV
3:30 PM – 4:30 PM
BALLROOMS 2 & 3

T1. Adolescent Nicotine Exposure Facilitates Punishment-Resistant Opioid Self-Administration and Increases Perineuronal Net Density Within Insular Cortex in Adulthood

Sarah Honeycutt, David Litche, Ashmita Mukherjee, Gregory Loney*

Adolescent nicotine exposure (ANE) is associated with enhanced liability for developing subsequent substance use disorders (SUDs) in adulthood. Insular cortex (IC) plays a critical role in contextual drug conditioning, is associated with development of compulsivity, and is modulated by nicotinic signaling. We have shown that ANE in rats engenders deficits in contextual opioid conditioning that resembles those seen following intra-IC nicotine infusions in adulthood. Relative to controls, ANE enhances conditioned place preference, and reduces conditioned taste avoidance of morphine-paired stimuli. Here, rats underwent ANE, operationalized as injections of 0.4 mg/kg nicotine (or saline), 2x day, from PND 34-43. At adulthood (PND 75), rats were trained to self-administer RMF (3.2 µg/kg) in two contexts, one in which drug infusions could be taken freely and another in which ~ 50% of infusions were punished with a foot-shock and intensity was escalated across sessions (0.1-0.7 mA). We found that ANE rats, relative to control, took more RMF in both the unpunished and punished contexts. We have previously shown this punishment-resistant phenotype is also expressed after acute nicotine injections in adulthood, suggesting that ANE produces persistent neurobiological changes that mimic the effects of acute nicotine pharmacology. Subsequently, we examined markers of neuronal plasticity in IC including the density of perineuronal nets (PNNs). PNNs are extracellular matrices commonly found surrounding cortical interneurons and play a role in restricting plasticity and decreasing behavioral flexibility. We found that ANE, relative to saline, significantly enhanced PNN density and increased the number of parvalbumin-expressing interneurons within IC. In summary, we demonstrate that ANE results in punishment-resistant drug-seeking and propensity to relapse as well as increased density of PNNs in IC, which appear to be associated with altered learning about opioid-associated cues.

T2. Chronic Ethanol Vapor Exposure in Adult Rats Reduces Behavior Flexibility

Yifeng Cheng, Patricia Janak*

Alcohol use disorder (AUD) is a neuropsychiatric disorder associated with persistent impairment in cognitive functions. Emerging evidence suggests chronic alcohol causes inflexible habitual alcohol-seeking behavior and impairs other flexible behavioral control. My previous studies showed that chronic alcohol evoked aberrant plasticity in the dorsomedial striatum (DMS) and impaired behavioral flexibility in updating action-outcome contingencies. However, the striatal neural activity underlying chronic alcohol-induced decision deficits is unclear. I hypothesized that animals with alcohol pre-exposure would show a reduced ability to adapt their behavior in non-stationary environments and that this behavioral dysfunction would be associated with distinct striatal activity patterns. To test this hypothesis, I used a dynamic probabilistic reversal learning task (dynaPRL), which allows the animal to experience different reward probability contrasts. To model human chronic binge drinking, I used the chronic intermittent ethanol vapor exposure (CIE) procedure to induce high blood ethanol levels (>150mg/dl) in Long Evan rats. Rats were then forced to abstain from ethanol and implanted drivable 16-channel electrodes into the striatum. I found that CIE rats showed a slower reversal speed compared to same-age air vapor (Air) controls when the reward probabilities reversed from a relatively high contrast context to a relatively low contrast context. Furthermore, CIE rats matched their choice more tightly to the local reward rate, indicating high exploitation behavior. Lastly, single-unit recordings revealed that an unrewarded choice inhibited a greater population of neurons in the DMS of CIE rats than in controls. This inhibitory effect is more profound in the post-reversal learning phase than in the pre-reversal stable phase. These results indicate that CIE rats may not process negative consequences properly, thus leading to a loss of adaptive control of action selection. To understand how CIE affects the updating process of the value function, I will employ a reinforcement learning model to compare the choice behavior between CIE and air controls qualitatively. Together these findings reveal behavioral and neural mechanisms underlying impairing effects of chronic alcohol on cognitive function.

T3. Striatal MORs Have Divergent Effects on Cocaine and Opiate Behaviors

Bailey Remmers, Carolyn Bowering, Miriam Bocarsly, Veronica Alvarez, Lauren Dobbs*

Regulation of striatal medium spiny neuron (MSNs) activity has been shown to regulate cocaine seeking and taking and the locomotor responses to cocaine. The mu opioid receptor (MOR) is a Gi-coupled receptor highly expressed in striatal MSNs and their activation restrains MSN activity and synaptic transmission. Global deletion of MORs reduces reinstatement of cocaine seeking, and intra-striatal MOR antagonists attenuate the expression and acquisition of cocaine place preference. It is unknown, however, which cell-specific population of MORs is responsible for mediating cocaine reward. To address this, we generated a cell-specific knockout of MORs from dopamine D2-receptor containing MSNs (D2-MORKO) and investigated how this affected cocaine conditioned place preference and locomotor responses. D2-MORKO mice showed slower acquisition of cocaine conditioned place preference and impaired expression of cocaine preference in the presence of acute cocaine administration. Additionally, cocaine-induced locomotor stimulation was heightened in D2-MORKO mice. In contrast, this selective MOR deletion had no effect on morphine or fentanyl place preference and locomotor stimulation. Our findings suggest a divergent role for MORs expressed in D2-MSNs in mediating cocaine and opiate reward and provide insight on striatal circuit mechanisms underlying behavioral responses to cocaine.

T4. Chemogenetic Excitation of the Lateral OFC Increases Likelihood of Risky Drug Taking Under Threat of Punishment

Zackari Murphy, Susan Ferguson*

Addiction is a disorder that can be characterized as the constant pursuit of a particular substance despite “negative” consequences. Physiological manifestations may explain this. Strides have been made to identify the brain areas that regulate risk taking, and the orbitofrontal cortex (OFC) has been identified as a primary candidate. Two divided subregions of the medial and lateral have been found to possess differing functions. The lateral portion is more affiliated with processing new information based on previous outcomes, as well as contingent and reversal learning. We found a decrease in neuronal activity in rats that decreased

their cocaine intake when it was associated with footshock punishment as indicated by cfos imaging. Animals that continued to take a high number of drug infusions despite footshock had higher counts of cfos in the lOFC. Thus, we propose that the amount of activity in the lOFC regulates the degree of risk-taking behavior an individual will engage in. In order to test this in this proposal, we used a viral strategy with DREADDs (an artificial receptor) that allows us to alter activity in the lOFC. Specifically, we compared increasing (hm3dq) or decreasing(hm4di) activity in the lOFC nonspecifically. The rats were placed in an intermittent access-based cocaine self-administration paradigm for 18 days total. Ten days were intermittent access to establish baseline , 4 days of punishment where each lever press had a 50% chance of a mild footshock upon infusion for a new measurement, and a final 4 days of punishment with the DREADD manipulation to monitor any correction in behavior. We found that inhibiting the lofc caused no change in pressing the lever under risk punishment when compared to punishment baseline. However, when we excited the region we not only noticed an increased likelihood of drug taking, but also drug seeking despite the threat of punishment as indicated by drug available and unavailable time periods. We followed up with a no punish self-administration paradigm to see if excitation would lead to increase taking or seeking in general. We did not notice a significant change compared to baseline nor control animals, leading us to believe the involvement of lOFC is context sensitive to influence decision making based on past outcomes, which is consistent with the literature.

T5. Extended Kappa-Opioid Receptor Antagonism Reduces Opioid Self-Administration in Dependent Mice

Lyndsay Hastings, Renata Marchette, Emma Frye, Erika Carlson, Leandro Vendruscolo, George Koob*

The dynorphin/κ-opioid receptor (κOR) system is a brain stress system that generally promotes dysphoria-, anxiety- and depression-like behavior. Dynorphin is upregulated in limbic brain regions during opioid dependence and is involved in opioid withdrawal-induced hyperalgesia, which is defined as an increase in pain sensitivity during opioid withdrawal. Hyperalgesia is hypothesized to contribute to drug taking and seeking through negative reinforcement. However, the direct role of the dynorphin-κOR system in opioid-related behaviors is not well understood. Here, we aimed to further our understanding of this system

by evaluating the effect of two κOR antagonists on fentanyl vapor self-administration (FVSA) in mice. We hypothesized that κOR antagonism would decrease FVSA. To test this hypothesis, we trained male and female C57BL/6J mice to self-administer vaporized fentanyl and split them between short-access (ShA; 1 h sessions) and long-access (LgA; 6 h sessions) groups. Mice tested in LgA sessions escalated their fentanyl intake, whereas those tested in ShA sessions did not. We tested the short-acting κOR antagonist aticaprant (0, 0.3, 1, 3, 10, 30 mg/kg, oral), which failed to reduce fentanyl self-administration in both the LgA and ShA groups. Following three weeks of abstinence, a single treatment with the long-acting κOR antagonist norBNI (10 mg/kg, intraperitoneal) significantly reduced the re-escalation of fentanyl in mice in LgA but not in ShA conditions. These data suggest that extended blockade of κORs is necessary to decrease opioid self-administration in dependent mice or that κORs are involved in the transition to opioid dependence rather than on established escalated drug intake. Further research will determine the efficacy of chronic treatment with short acting κOR antagonists in reducing opioid self-administration and whether long acting κORs antagonists reduce previously escalated drug intake.

T6. Individual Vulnerability to Predator Scent Stress Enhances Oxycodone-Seeking in Rats

Courtney Wilkinson, Marek Schwendt, Lori Knackstedt*

The prevalence of opioid use disorder (OUD) remains at a crisis level in the U.S. Treatment for OUD is complicated by comorbidities, such as posttraumatic stress disorder (PTSD). A rodent model that captures the individual differences in stress-susceptibility exhibited by humans is necessary in order to understand the neurobiology of comorbid PTSD+OUD. The present study sought to develop such a model, utilizing predator scent stress followed by oxycodone self-administration, extinction training, and a cue-primed reinstatement test. Thirty-six Sprague Dawley rats (half male) received a single 10-minute exposure to the fox pheromone 2,5-dihydro-2,4,5-triethylthiazoline (TMT) in an inescapable chamber. Seven days later, rats were assessed for hypervigilance- and anxiety-like behavior using the acoustic startle response (ASR) and elevated plus maze (EPM), respectively. Using a double median split analysis of time spent in the open arms of EPM and habituation to acoustic startle in ASR, rats were classified into stress-Susceptible (PTSD-like), -Resilient, or Intermediate phenotypes. Rats were implanted with jugular catheters and underwent self-

administration of intravenous oxycodone (0.1 mg/kg/infusion) for 6 days on a fixed ratio-1 (FR-1) schedule of reinforcement followed by 6 days on an FR-3 schedule. Rats underwent extinction training for 14 days before cue-primed reinstatement testing. Stress-Susceptible rats exhibited greater oxycodone intake, increased presses on the lever that previously delivered drug during extinction training, and greater reinstatement of oxycodone-seeking relative to stress-Resilient and control rats. We will examine the relationship between oxycodone-seeking and cFos expression in subregions of the mesocorticolimbic system. For the first time, we show that susceptibility to predator scent stress confers enhanced oxycodone-seeking, suggesting that this may be a valuable model for identifying future drug targets for these comorbid disorders.

T7. Kappa Opioid Control of a GABAergic Stress-Sensitive Circuit Involved in Reinstatement

Valentina Martinez Damonte, Julie A. Kauer*

The VTA is a brain region necessary for drug reinforcement. Plasticity at GABAergic synapses controlling dopamine neuron excitability is a target of drugs of abuse and acute stress. We have previously shown that a single acute exposure to cold-water swim stress induces reinstatement of cocaine seeking via kappa opioid receptor (kOR) activation. We also found that this stressor blocks nitric oxide-induced potentiation of inhibitory postsynaptic currents (LTPGABA) onto VTA dopamine cells. Here we began to identify the kOR and dynorphin circuit elements responsible for the block of LTPGABA. Stress-induced block of LTPGABA relies on activation of kOR and hence deleting kORs from the relevant cell type should prevent this. Using a conditional knock-out approach, we found that kORs in dopamine cells are not required for stress-induced loss of LTPGABA. This suggests that the relevant kORs are instead located on presynaptic terminals. We found that GABAergic afferents from nucleus accumbens (NAc) undergo LTPGABA, and furthermore selectively deleting kORs from these terminals prevents stress-induced block of LTPGABA. To identify the dynorphin sources relevant for stress-induced block of LTPGABA, we have begun to drive individual sets of dynorphin afferents to the VTA to induce dynorphin release in brain slices and test for the presence of LTPGABA. Over the last few decades, it has become clear that VTA dopamine neurons are highly heterogeneous and participate in distinct circuits that are differentially modulated. To test whether dopamine neurons projecting

to either NAc or prefrontal cortex participate in subcircuits sensitive to stress, we are injecting retrobeads in these brain nuclei and testing for LTPGABA in these dopamine neuron subpopulations. Our work contributes to defining the circuit involved in stress-induced reinstatement and highlights the importance of inhibitory inputs for controlling dopamine neuron excitability in the context of addiction.

T8. Measuring Activity in Corticostriatal Neuronal Ensembles From the Onset of Heroin Use to Relapse

Rachel Clarke, Sophie Buchmaier, Shannon Woods, Kelsey Vollmer, Elizabeth Doncheck, Kion Winston, Roger Grant, Jacqueline Paniccia, Michael Martino, Amy Ward, Michael Scofield, James Otis*

Both clinical and preclinical studies have reproducibly demonstrated that communication between the prelimbic cortex and the nucleus accumbens core (PrL-NAcc) is critically involved in the reinstatement of heroin seeking. Further, preclinical studies show that PrL-derived glutamate release in the NAcc is required for relapse to drug seeking. While the importance of the PrL-NAcc circuit has been established, very little is known about the in vivo dynamics of PrL-NAcc neurons. Specifically, how PrL-NAcc neuronal ensemble dynamics evolve over the course of heroin use, are engaged during relapse to drug seeking, and functionally orchestrate relapse behavior remains unknown. Here we use in vivo two-photon imaging coupled with a head-fixed mouse heroin self-administration (SA) paradigm to investigate these neuronal adaptations during heroin self-administration, extinction, and reinstatement. Firstly, to confirm that the PrL-NAcc is necessary for reinstatement of heroin seeking in our head-fixed mouse heroin SA paradigm, we used pathway specific optogenetics (via AAVrg-cre and AAV-DIO-ef1a-eNpHR3.0 or DIO-eYFP) to inhibit the cell bodies of PrL-NAcc projecting neurons during reinstatement testing. Following 14 days of heroin SA and 10 days of extinction, light-mediated inhibition of PrL-NAcc neurons (eNpHR3.0) significantly supressed lever pressing during cue-, drug-, and TMT- (predator odor) primed reinstatement compared to control (eYFP) animals. Next, we used two-photon calcium imaging to observe the dynamics of PrL-NAcc neurons (via AAVrg-cre and AAV-DIO-GCaMP6M) throughout acquisition, extinction and reinstatement of heroin seeking. We have identified distinct neuronal ensembles within the PrL-NAcc neurons that encode specific information relevant to 1) operant responding for a heroin reward, 2) delivery of a heroin associated cue and 3) infusion of a heroin

reward. Having identified specific PrL-NAcc neuronal ensembles encoding reinstatement of heroin seeking, our ongoing efforts aim to utilize single-cell optogenetics to manipulate these ensembles during a reinstatement test to determine if disrupting specific subpopulations of neurons in the PrL-NAcc circuit is sufficient to supress heroin seeking.

T9. Multiomic Profiling of the Rat Nucleus Accumbens Reveals Cell-Type Specific Chromatin Remodeling and Transcriptional Alterations After Cocaine Experience

Jennifer Tuscher, Robert Phillips III, Lara Ianov, Sasha Fulton, Ian Maze, Jeremy Day*

Cocaine use elevates dopamine levels in the nucleus accumbens (NAc) to initiate cell signaling cascades that engage transcriptional machinery and promote enduring synaptic and behavioral adaptations. These long lasting changes in gene expression in the NAc are thought to be mediated in part by chromatin reorganization within cocaine-affected cell populations. Prior studies profiling bulk NAc tissues have identified widespread changes in chromatin-associated proteins, histone modifications, and DNA methylation following cocaine experience. However, little is known regarding how cocaine intake alters chromatin dynamics in a cell-specific manner within the NAc, or how long these changes persist after cessation of drug use. Here, we used a cocaine intravenous self-administration (IVSA) model to profile long-lasting chromatin and transcriptional alterations induced by cocaine with single-cell resolution in a rat model system. We observed previously described features that model aspects of human substance use disorders (SUDs), including escalation of intake across acquisition and increased cocaine seeking following 30 days of withdrawal. Multiomic profiling with single-nucleus RNA sequencing (snRNA-seq) and single-nucleus Assay for Transposase Accessible Chromatin (snATAC-seq) on 39,325 nuclei from the rat NAc after withdrawal confirmed previously identified neuronal and non-neuronal cell types in the NAc. Comparison of open chromatin regions between annotated cell types revealed thousands of cell-selective regulatory elements, many of which are linked to genes previously implicated in SUDs and motivated behavior. Further, this dataset revealed enduring and cell-specific chromatin alterations present 30 days after withdrawal. These results provide key insights into how cellular diversity contributes to chromatin remodeling and transcriptional alterations following cocaine use, and suggest the

the importance of cell-type specific genomic regulation in the progression of SUDs.

T10. Ex Vivo Optical Imaging of Calcium and Dopamine Dynamics in Primate Ventral Tegmentum Reveals Synaptic Plasticity Signatures of Chronic Ethanol-Induced Cognitive Dysregulation

Kirsty Erickson, Suzanne Nolan, Zahra Farahbakhsh, Wilson Adams, Verginia Cuzon Carlson, Kathleen Grant, Cody Siciliano*

Ethanol is one of the most widely used compounds and poses an immense global health burden, with 5.3% of worldwide deaths attributed to alcohol consumption. Progressive deficits in cognitive flexibility are a primary sequelae of alcohol use disorders (AUD) and the severity of ethanol-induced cognitive deficits predict disease trajectory and treatment responsivity. Though long-standing evidence suggests that cognitive dysfunction is a defining characteristic of AUD, mechanistic investigations of the underlying synaptic and circuit mechanisms mediating ethanol-induced cognitive dysregulation are limited, in part due to the lack of animal models that holistically recapitulate ethanol drinking behaviors and cognitive readouts in tandem. Recently, we have developed a novel approach for achieving viral-mediated gene expression in acute ex vivo brain slice preparations, permitting high-fidelity imaging of optical biosensors in genetically intractable species, including primates, without the requirement of germline editing or prior in vivo manipulations. Here, we implement this approach to simultaneously resolve dopamine and calcium dynamics in the ventral tegmental area of rhesus macaques following two years of cognitive testing and ethanol self-administration (N=12, 6 male, 6 female). Our results show the utility of this method to examine basic neurophysiological questions in NHP brain slices, reveal the neural correlates of individual differences in drinking behavior using a chronic ethanol self-administration model, and elucidate the neurochemical effects of salsolinol, a secondary ethanol metabolite and condensation product of acetaldehyde and dopamine, on VTA cell excitability and dopamine dynamics. Not only do these experiments offer great utility for the alcohol field, but they also provide a powerful framework for testing the generalizability of neurobiological findings across multiple species.

T11. Neuronal Correlates of Hyperalgesia and Somatic Signs of Heroin Withdrawal in Male and Female Mice

Yocasta Alvarez-Bagnarol, Renata Marchette, T Chase Francis, Marisela Morales, Leandro Vendruscolo*

Opioid withdrawal involves the manifestation of motivational and somatic symptoms. However, the brain structures that are involved in the expression of different opioid withdrawal signs remain unclear. We induced opioid dependence by repeatedly injecting escalating heroin doses in male and female C57BL/6J mice. We assessed hyperalgesia during spontaneous heroin withdrawal and somatic signs of withdrawal precipitated by the preferential m-opioid receptor antagonist naloxone. Heroin-treated mice exhibited significantly higher hyperalgesia and somatic signs than saline-treated mice. Following behavioral assessment, we measured regional changes in brain activity by automated the counting of c-Fos expression (a marker of cellular activity). Using Principal Component Analysis, we determined the association between behavior (hyperalgesia and somatic signs of withdrawal) and c-Fos expression in different brain regions. Hyperalgesia was associated with c-Fos expression in the lateral hypothalamus, central nucleus of the amygdala, ventral tegmental area, parabrachial nucleus, dorsal raphe (DR), and locus coeruleus (LC). Somatic withdrawal was associated with c-Fos expression in the paraventricular nucleus of the thalamus, lateral habenula, DR, and LC. Thus, hyperalgesia and somatic withdrawal signs were each associated with c-Fos expression in unique sets of brain areas. The expression of c-Fos in the DR and LC was associated with both hyperalgesia and somatic withdrawal. Understanding common neurobiological mechanisms of acute and protracted opioid withdrawal may help identify new targets for treating this salient aspect of opioid use disorder.

T12. 3D Optogenetic Interrogation of Prelimbic Reward Learning Ensembles

Roger Grant, Elizabeth Doncheck, Kion Winston, Kelsey Vollmer, Jacqueline Paniccia, Rachel Clarke, Sophie Buchmaier, James Otis*

The prelimbic sub region of the dorsomedial prefrontal cortex is a critical structure that coordinates learned reward-seeking behavior in mice. However, at the single cell and population level, the prelimbic cortex exhibits heterogeneous activity patterns during reward seeking. Recently, we characterized five functional neuronal ensembles in the prelimbic cortex based on their coordinated activity during a Pavlovian sucrose seeking task. Furthermore, we showed that the activity of these ensembles is stable across days and differentially encodes specialized information related to the task. Given the robust information encoding by these ensembles, we hypothesized that by disrupting their activity, we could uncover the influence of each ensemble on natural reward-seeking behavior. Using mice which co-express a calcium indicator (AAVdj-CaMKIIα-GCaMP6s) and red-shifted excitatory opsin (AAVdj-CaMKIIα-ChRimson) in prelimbic excitatory output neurons, we performed concurrent in vivo two-photon calcium imaging and single-cell optogenetics while mice engaged in a Pavlovian sucrose seeking task. Using this approach, we were able to simultaneously stimulate multiple cells from the same ensemble in three dimensions while monitoring population calcium dynamics. Our preliminary results indicate that activation of as few as three cells from an ensemble that encodes licking is sufficient to influence conditioned licking behavior. In ongoing experiments, we are targeting other ensembles, including those that encode cue discrimination, and reward availability to determine their influence on reward seeking in our task. In this way, we hope to elucidate neuronal subpopulations in prelimbic cortex which influence the expression of learned reward-seeking behavior.

T13. Assessing the Effects of ΔFOSB Induction on the in Vivo Activity of Nucleus Accumbens Medium Spiny Neurons

Tamara Markovic, Arthur Godino, Eric Parise, Leanne Holt, Gyles Trevor, Eric J. Nestler*

ΔFOSB is a key transcription factor that mediates gene expression changes in the nucleus accumbens (NAc) in response to chronic exposure to stress or drugs of abuse. The NAc is composed of GABAergic medium spiny neurons (MSNs) that express either dopamine

receptor 1 (D1) or dopamine receptor 2 (D2). Previous work in rodents showed that chronic exposure to different stimuli induce ΔFOSB in the NAc in a cell-type-specific manner: cocaine mainly induces ΔFOSB in D1 MSNs, chronic stress induces the protein in D2 MSNs in stress-susceptible but in D1 MSNs in stress-resilient animals, while natural rewards induce ΔFOSB in D1 and D2 MSNs. This cell-type-specific regulation of ΔFOSB expression in the NAc correlates with differential effects of the protein on synaptic properties of MSNs: ΔFOSB decreases excitatory synaptic strength and increases silent synapses onto D1 MSNs, with opposite effects seen for D2 MSNs. However, no studies have investigated how changes in ΔFOSB expression levels in the NAc alter the in vivo activity of MSNs. To address this gap in knowledge, we injected D1-Cre and D2-Cre mice with Cre-dependent adeno-associated viral vectors that express a calcium sensor and epigenome-editing tools that either induce or repress endogenous ΔFOSB in the NAc. We recorded in vivo neuronal activity of D1 and D2 MSNs using fiber photometry in response to social reward, saccharin reward, foot shock, and drug rewards. Our preliminary findings demonstrate that repression of ΔFOSB increases calcium transients in D1 MSNs upon social interaction, while induction of ΔFOSB increases calcium transients in D2 MSNs in the same assay. We found similar result in response to saccharin reward in self-administration. This finding of opposite in vivo modulation of D1 vs. D2 MSN activity by ΔFOSB relates the downstream consequences of transcriptional regulation to altered circuit activity and will help delineate how such cell-autonomous mechanisms control complex behavioral responses.

T14. Dopamine and Calcium-Indicated Activity in the Dorsal Striatum During the Transition to DLS Dopamine-Dependent Cocaine Seeking and Pavlovian Cue Extinction

Brooke Bender, Sierra Stringfield, Mary Torregrossa*

A preclinical model of cue exposure therapy, cue extinction, reduces cue-induced cocaine seeking when drug seeking is goal-directed and reliant on the dorsomedial striatum (DMS), but not when behavior is habit-like and reliant on the dorsolateral striatum (DLS). As control of drug seeking shifts within the dorsal striatum, it is unclear how neural activity and dopamine release in the dorsal striatum changes. Additionally, the effects of cue extinction on dorsal striatum cue- and drug-seeking-induced activity have not been investigated.

The fluorescent calcium indicator jRCaMP1b and the dopamine indicator dLight1.2 were expressed in the DLS and DMS of male and female rats. Rats were trained to self-administer cocaine intravenously paired with an audiovisual cue. After acquisition, fiber photometry was used to record changes in calcium- and dopamine-indicated fluorescence in the DLS and DMS during 15-minute drug-seeking tests prior to daily self-administration. Rats were trained to facilitate goal-directed or habitual behavior, and after training rats underwent cue extinction (non-contingent exposure to 120 cues) followed by a cue-induced drug-seeking test. When cue-reinforced active lever presses where compared to unreinforced active lever presses or inactive lever presses, both the DLS and DMS showed increased calcium and dopamine activity. As training progressed, both groups showed increased dopamine activity in the DMS and DLS, and there was an interaction where calcium activity in the DMS increased for goal-directed rats but decreased for habitual rats. Noncontingent cues did not result in increased dopamine activity, but did cause small increased in DMS and DLS calcium that were reduced by the end of cue extinction. After cue extinction, both groups showed a reduction in dopamine activity in the DMS in response to cue-reinforced lever presses. These findings are the first to report dopamine and calcium activity in the DMS and DLS as behavior becomes habitual.

T15. A Subset of Dorsal Raphe Glutamatergic Neurons Relays Rewarding Information to the Ventral Tegmental Area

Rodrigo Osnaya, Qianwei Shen, Huiling Wang, Liu Bing, Shiliang Zhang, Marisela Morales*

The Ventral Tegmental Area (VTA) plays a role in different aspects of motivated behavior, mediated in part by dopamine neurons that integrate information from different brain structures. We had previously demonstrated that subsets of Dorsal Raphe (DR) glutamatergic neurons expressing the vesicular glutamate transport 3 (VGluT3) establish excitatory synapses on VTA dopaminergic neurons, and the involvement of this pathway in reward. Here, we present evidence indicating that in addition to DR-VGluT3 inputs to VTA, there is another source of DR glutamatergic neurons, expressing the vesicular glutamate transporter 2 (VGluT2) that innervates the VTA. By VTA injection of the retrograde track tracer FluoroGold (FG) and phenotyping of DR-FG-neurons, we detected DR-FG-neurons expressing VGluT2 mRNA concentrated in the laterodorsal aspects of the DR, these DR-FG neurons represent ~40% of

the total population of FG-neurons, indicating that the subset of DR-VGluT2 neurons provide a major input to VTA. Next, to investigate a possible role of DR-VGluT2 pathway to VTA in behavior, we injected a cre-dependent viral vector in the DR of VGluT2-cre mice to selectively expressed ChR2-tethered to eYFP under the regulation of the VGluT2 promoter in DR-VGluT2 neurons. By immunohistochemistry, we confirmed VTA expression of eYFP-axons from DR-VGluT2 neurons, and by VTA laser-stimulation found that mice presented a preference for a chamber in which they received the laser stimulation. By intra-optical cranial self-stimulation, we found that mice preferred to turn a wheel associated with VTA-laser-stimulation of DR-VGluT2 inputs. Thus, further indicating that DR-VGluT2 inputs to VTA participate in reward processing. Next, we determined the extent to which DR-VGluT2 neurons innervating the VTA changes in response to a reward. For these studies, we injected a Cre-dependent retrograde GCaMP virus within the VTA of VGluT2-Cre mice and implanted a photometry fiber on the DR. We found that DR-VGluT2 neurons innervating the VTA increased their activity in response to sucrose consumption. In summary, while DR is best known to regulate behavior by releasing serotonin throughout the brain, we discovered an unanticipated subset of DR excitatory VGluT2-neurons that relay reward and salience signaling to VTA by releasing glutamate.

T16. Characteristics of DMPFC Astrocyte Dynamics During Natural- and Drug-Reward Seeking Behaviors

Jacqueline Paniccia, Roger Grant, Elizabeth Doncheck, Rachel Clarke, Sophie Buchmaier, Elizaveta Romanova, Annaka Westphal, Kelsey Vollmer, Michael Martino, Amy Ward, Kion Winston, James Otis, Michael Scofield*

Unique neuronal ensembles within the dorsomedial prefrontal cortex (dmPFC) encode specialized information pertaining to reward-associated cues, reward delivery, and reward seeking behaviors in both natural- and drug-reward learning tasks. Astrocytes critically modulate neuronal dynamics, and drug-induced adaptations in their ability to regulate synaptic plasticity in the nucleus accumbens are required for cue-induced reinstatement of heroin seeking. However, how astrocytic activity patterns in other brain areas adapt across reward learning remains unknown. Using in vivo two-photon imaging, we longitudinally measured dmPFC astrocytic calcium (Ca2+) dynamics across reward learning in both Pavlovian sucrose conditioning and heroin self-

administration (SA) and relapse. First, mice were head-restrained and trained to predict one tone conditioned stimulus (CS+), but not another (CS-), with sucrose delivery. After training, mice displayed anticipatory licking between CS+ onset and sucrose delivery, indicative of cue-reward learning. Notably across learning, dmPFC astroglial activity was increased in CS+ trials, temporally paralleling the CS+ and sucrose pairing. We found dmPFC astrocytes were most active following the CS+ and sucrose pairing, with decreased responses evoked by either CS+ or sucrose alone. These data indicate that dmPFC astrocytes participate in encoding the cue-sucrose association. We then assessed how dmPFC astroglial activity adapts across heroin seeking. Mice underwent our head-fixed SA, extinction, and reinstatement protocol. Briefly, animals learned that responses on the active lever result in presentation of a tone (CS+) and subsequent heroin infusion, linking the CS+ to drug availability. We found dmPFC astrocytes display biased activation towards active press/CS+ and drug delivery during active taking, and cue presentation during relapse. These studies are the first to examine dmPFC astroglial activity across both natural- and drug-reward seeking.

T17. Effects of Sex and Age on Nicotine Vapour Reward, Withdrawal, Pharmacokinetics, and Brain Activity

Jude Frie, Patrick McCunn, Ahmad Hassan, Karling Luciani, Chuyun Chen, Rachel Tyndale, Jibran Khokhar*

Introduction: Nicotine use has seen drastic change in recent years with drastic increases in vaping as a method of nicotine delivery. Much is still unknown about the effects of nicotine vapour on vulnerable populations. Our objective was to characterise the sex- and age-dependent effects of nicotine vapour exposure. We hypothesise that nicotine vapor would differentially effect behaviour, pharmacokinetics and functional connectivity.
Methods: Passive nicotine exposures were conducted via JUUL e-cigarettes in a custom built vapour chamber. Animals were evaluated for reward-like behaviour in a place conditioning paradigm, locomotion in an open field, precipitated withdrawal following i.p. mecamylamine injection (1.5 mg/kg), nicotine and nicotine metabolite brain and plasma pharmacokinetics, and functional magnetic resonance imaging.
Results: Female but not male adults acquired conditioned place preference (CPP) at a high dose of nicotine vapour. Female adolescents did not acquire CPP at any dose tested. Both adult and adolescent

males displayed similar levels of precipitated nicotine withdrawal. Female rats did not display any precipitated nicotine withdrawal. Nicotine plasma and brain levels were similar between adults and adolescents, although females did show higher plasma nicotine plasma levels at 10 minutes compared to adolescent females. Adult females had greater nicotine concentrations than adult males in both plasma and brain. This trend was similar in adolescent female brain supernatant but not plasma where results were not significantly different. Functional MRI revealed a single network consisting of 12 edges and 13 nodes that displayed reduced connectivity when controlling for age and sex. An additional significant group by sex interaction effect was found with 5 edges and 6 nodes showing further reduced connectivity in females compared to males.
Conclusions: Our findings suggest that nicotine vulnerability is affected by sex and age, with unique behavioural and pharmacokinetic profiles, and functional changes in regions involved in nicotine cue reactivity, withdrawal, and dependence.

T18. Adolescent Nicotine Enhances Adult Morphine Reward by Altering Ventral Tegmental Area GABA Circuits

Ruthie Wittenberg, Olivia Swanson, Sanghee Yun, Amelia Eisch, John Dani*

Opioid use disorder is an immense source of preventable mortality and economic burden in the U.S. An important, but poorly understood, risk factor is previous nicotine use. Epidemiological evidence suggests that adolescent nicotine acts as a gateway drug and increases vulnerability to subsequent drug use, including to morphine. However the neural mechanisms underlying this interaction remain unknown. Prior work in rodents has reported that the effects of adult nicotine on VTA circuitry and on drug reinforcement behavior are prolonged if the nicotine is administered during adolescence. This suggests that adolescence is a vulnerable developmental stage during which nicotine-related plasticity can be maintained into adulthood and thereby exert long-lasting influence over later-life drug use. To test the effect of adolescent nicotine on adult morphine reward, we exposed male and female adolescent mice to nicotine in their drinking water for two weeks (0.1 mg/mL on Days 1-5; 0.2 mg/mL on Days 6-14) and probed both behavioral- and circuit-level adaptations to morphine in adulthood.

Adult mice that received nicotine during adolescence showed enhanced preference for the morphine-paired chamber in a morphine conditioned place preference (CPP) paradigm relative to controls that received plain drinking water. Adolescent nicotine mice also consumed more morphine in a two-bottle choice drinking task and demonstrated increased morphine locomotor sensitization in adulthood. These behavioral changes corresponded with alterations in VTA GABA signaling. Following adolescent nicotine, VTA GABA neurons exhibited a depolarizing shift in the GABAA reversal potential and paradoxically heightened action potential firing in response to morphine. Finally, to test whether this increase in inhibitory activity in the VTA may be a causal mechanism underlying the enhanced morphine reward, we chemogenetically inhibited VTA GABA neurons during morphine CPP and found a reduction in the heightened preference for the morphine chamber among the adolescent nicotine mice. Among the adolescent water mice, inhibition of VTA GABA neurons increased preference for the morphine chamber. Together these data reveal that adolescent nicotine promotes morphine reward in adult mice and that this may be driven by an increase in VTA GABA activity.

T19. The Role of GPR171 in Depression in Females

Megan Raddatz, Callie Porter, Erin Bobeck*

Depression is the most common mental health disorder in the United States. Of the estimated 25 million afflicted individuals, over two-thirds are female, indicating a potential role of sex hormones in the etiology and treatment of depression. Critically, new treatments are needed that specifically address the efficacy of antidepressants in females. One source of potential novel treatments is G-Protein Coupled Receptors (GPCRs) which are receptors capable of a broad range of responses and play a role in nearly every physiological process. Of particular interest is GPR171, a recently deorphanized receptor that modulates pain, feeding, and anxiety. Preliminary data in our lab indicated that agonism of GPR171 led to a slight decrease in depressive behaviors in female mice in the forced swim test (FST) but the results were unclear due to potential hormonal interactions. Thus, the aim of our experiment was to determine if GPR171 agonism led to a reduction in depressive-like behaviors in female mice while controlling for estrogen. To this end female mice underwent ovariectomy surgery to remove the ovaries and control for endogenous hormone fluctuations. Two weeks later, mice

were injected with either estrogen or a placebo once a day for four days. On the final day of hormonal injections mice were also injected with either a GPR171 agonist or vehicle. Following the final injection mice were subjected to the FST to assess depression/behavioral despair. Immobility in the FST was recorded by two independent scorers blind to the drug and hormone treatment. Results indicate that the agonist paired with placebo decreased immobility time in the FST representing a reduction in depression-like behaviors when compared to vehicle-treated mice. However, under the estrogen treatments this effect was not present, indicating an interaction of the agonist and estrogen. Together, these findings identify a GPR171 agonist as a potential pharmaceutical target for depression in female mice.

T20. The Ventral Hippocampus is Necessary for Trauma Enhanced Aggression (TEA)

Kevin Sattler, Raina Miller, Moriel Zelikowsky*

A single, acute traumatic experience can result in a host of negative behavioral effects, such as increased aggression and inappropriately elevated fear to non-noxious stimuli. Despite the large body of research on ways trauma can alter the brain, we nevertheless have a poor understanding of how the brain both encodes trauma and consolidates associated changes in behavior. The hippocampus is well-suited for processing the behavioral effects of trauma. Indeed, it sits in an ideal anatomical position – receiving inputs from sensory integration sites and sending output to regions involved in social and emotional behavior. Moreover, the ventral hippocampus (VH) has been implicated in emotional processing. The VH has wide ranging projections to the prefrontal cortex, amygdala, and hypothalamus, among others, suggesting a diverse role in modulating behavioral output. For example, the VH projects to the basolateral amygdala (BLA), known for its involvement in fear modulation and the ventromedial hypothalamus (VMH), which has been implicated in increased aggression. By chemogenetically silencing the VH during an aggression/social interaction assay, we show that the VH is necessary for trauma-enhanced aggression. To further dissect the involvement of neuronal ensembles in the VH to encode the effects of trauma on both enhanced fear and enhanced aggression, we will determine whether ensembles activated by each phenotype have unique projection profiles using viral tracing and immunohistochemistry. This study will investigate a possible role for the VH as a central hub underlying trauma-altered

social behaviors and provide insight into how experiencing a traumatic event can lead to diverse behavioral changes.

T21. Persistent Epigenetic Mediated Paternal Transmission of Stress Phenotypes to Offspring Show Brain Region-Specific Transcriptomic Signature

Ashley Cunningham, Deena Walker, Aarthi Ramakrishnan, Orna Issler, Hannah Cates, Li Shen, Eric Nestler*

Poster Abstract Depression risk has long been known to be highly influenced by both genetic and environmental factors. More recently, it has been proposed that epigenetic mechanisms may also contribute, representing a third basis of risk. Previous studies on intergenerational trauma in rodents from our lab have shown that resilient and susceptible fathers exposed to chronic social defeat stress (CSDS) have different patterns of behavioral transmission and transcriptional changes in sperm. However, no studies to date have examined the persistent transmission of stress phenotypes to multiple litters in fathers from resilient and susceptible lineages. To study this, F0 male mice were exposed to 10 days of CSDS and subjected to social interaction testing to assess paternal phenotype (resilient or susceptible). Resilient, susceptible, or control F0 males were allowed to mate 30 days after stress to produce F1 Litters 1 and again 60 days following stress to produce F1 Litters 2. We found that while both resilient and susceptible fathers persistently transmitted altered stress phenotypes to female F1 offspring, only susceptible fathers persistently transmitted altered stress phenotypes to male offspring. To better understand how the transcriptome in brain regions involved in stress response may be differentially responding to stress in F1 offspring from stress lineages compared to controls, we conducted RNAsequencing of the prefrontal cortex (PFC) and nucleus accumbens (NAc). We found that the PFC but not the NAc shows stress lineage specific dynamic changes in response to stress in F1 offspring. Finally, using a combination of bioinformatic techniques we identify key genes in the PFC that may be involved in regulating the behavioral phenotypes seen in male and female offspring from stress lineages. Taken together, these studies advance our understanding of the intergenerational epigenetic transmission of behavioral experience.

T22. Modulation of Ventral Pallidum Arkypallidal Neuron Activity by Corticotrophin Releasing Factor (CRF) Signaling

Elizabeth Souter, Lucy Anderson, Julia Lemos*

The ventral pallidum (VP) is a basal ganglia structure involved in hedonic evaluation, integration of internal and external cues, and motivated behaviors. There is a ventral arkypallidal (vArky) VP population which sends inhibitory projections to the nucleus accumbens (NAc). Optogenetic stimulation of vArky VP neurons promotes reward consumption. Thus, mechanisms by which experience may modulate this circuit are important to our understanding of reward-related behaviors. Corticotropin releasing factor (CRF) signaling has been shown to mediate many stress-related behaviors. We have identified a subpopulation of VP neurons expressing CRF receptor type 1 (CRF1). Using dual in situ hybridization and immunohistochemistry, we quantified the co-localization of Crhr1 (CRF1) RNA with Slc32a1 (VGAT), Slc17a6 (VGLUT2), or Chat (ChAT) in VP neurons. We found that 76% of VP CRF1+ neurons are GABAergic, with a smaller proportion of glutamatergic (21%) and cholinergic (6%) cells. We next examined the projection targets of VP CRF1+ cells using a Cre-dependent viral vector expressing synaptophysin-fused mRuby into VP of Crhr1Cre mice. We found that VP CRF1+ cells preferentially synapse in NAc, with very few synaptic contacts in ventral tegmental area or lateral habenula, which suggests that CRF1 is expressed preferentially on vArky neurons. To examine the functional consequence of CRF1 activation in VP, we used ex vivo slice electrophysiology to record from VP CRF1+ cells at baseline and following bath application of CRF. We found that CRF application was able to modulate the excitability of CRF1+ VP neurons. Finally, we examined cFos expression in VP in stress-naïve and swim-stress exposed mice. We found that stress was able to induce an increase in cFos in the VP, indicating increased activation of this region following stress exposure. Taken together, these findings outline a mechanism through which stress may modify VP function and, thus, modulate motivated behaviors.

T23. Connecting -omics Across Tissues in Fragile X Syndrome

*Sabiha Alam, Clay Prater, Puni Jeyasingh, Babu Fathepure, Edralin Lucas, Elizabeth McCullagh**

Fragile X Syndrome (FXS) is the most commons genetic form of autism. FXS has no cure, but therapeutic interventions can help mitigate the behavioral and physiological health complications caused by the disorder. A whole-body approach integrating phenotypes across integrated systems is needed to not just treat neurological symptoms but understand the complexities of interactions between bodily systems. We have performed experiments that measure elemental abundance across the brain and gut, and bone and metabolite composition across tissues, to better understand and ultimately treat underlying imbalances in FXS. Ionomics is a new multidisciplinary field integrating the study of the ionome, or the composition of mineral and trace elements essential for homeostatic function found in all living organisms. Our preliminary data of the whole brain ionome of FXS and wildtype mice showed an association between calcium (Ca) concentration and genotype, where the mean Ca level was comparatively higher in Fmr1 KO mice than control and heterozygous mice. While PCA showed no significant relationship between genotype and specific ions individually, they do suggest that FXS mice have increased sulfur, calcium, sodium, potassium, phosphorus, and lithium compared to wildtype. Our ionome results of the cecum also showed significantly higher Si, Ca, and B compared to wildtype with sex specific differences including higher Ni, Mn, and Cu in females compared to males independent of genotype. Initial results show significant increases in bone mineral density (BMD) and decreased percent fat in FXS mice compared to wildtype somewhat consistent with other's work showing decreased fat percentage. Future work is planned to measure gut microbiome and metabolite composition in the same animals as ionome and bone measurements are taken to characterize the whole-body phenotype of FXS mice. Lastly, we intend to use these results to inform a nutritional supplement to test core symptoms of FXS. This research informs insights on whole body function in FXS and the underlying elemental, microbial, and organ level changes at the core of complex behaviors.

T24. Abnormal Ensemble Activity Underlies Pathologic Changes in Social Behavior in Shank3 Mice

Nicholas Frost, Kevin Donohue, Vikaas Sohal*

Abnormal social interactions are a hallmark feature of autism spectrum disorders and are recapitulated in preclinical models of these heterogeneous disorders. Underlying this abnormal behavior are changes in microcircuit structure and function, however it is unknown how changes in excitation or inhibition might alter how information is encoded during behavior. We sought to understand at a multineuron or ensemble level how information pertinent to different behaviors such as social interaction are encoded in the medial prefrontal cortex (mPFC). We then investigated how this encoding might be altered in a mouse model of autism lacking the postsynaptic scaffolding molecule Shank3. We show that underlying social interaction are dynamic changes in the activity of single neurons and ensembles which are specifically active during social interaction, and distinct from those activated during anxiety-related behaviors. Mice lacking Shank3 have hyperdynamic network responses characterized by abnormally increased neurons which are positively modulated and fewer neurons which are negatively modulated compared to wildtype mice. Finally, we show that these hyperdynamic network responses result in loss of encoding by multineuron patterns during behavior. We propose that this less efficient and imprecise computation likely results in deficits in information routing across distributed circuits during behavior.

T25. Potentiation of the M1 Receptor Exerts Therapeutic Effects in a Mouse Model of Rett Syndrome

*Mackenzie Smith, Jakub Cikowski, Grace Dodis, Calista Holt, Sonia Gonzalez, Colleen Niswender, Rocco Gogliotti**

Rett syndrome (RTT) is a neurodevelopmental disorder that results from mutations in a methyl-reader protein known as Methyl CpG Binding Protein 2 (MeCP2). Patients with RTT present with developmental regression, stereotyped hand movements, loss of communicative ability, and central apneas. Previously, we reported significant decreases in muscarinic acetylcholine receptor (mAChR) expression in motor cortex and cerebellum samples from RTT patients. We now show that decreased mAChR subtype 1 (M1) expression is a highly penetrant aspect of the disease in 40 RTT autopsy samples and that M1 mRNA levels directly

correlate with MeCP2 dosage. We further demonstrate that acute treatment with an M1 positive allosteric modulator (PAM, VU0453595) improves social, cognitive, and respiratory phenotypes in a Mecp2+/- mouse model of RTT. RNA sequencing data from Mecp2+/- mice treated with VU0463595 suggests that efficacy on respiratory phenotypes may be linked to the assembly and presentation of NMDARs in the brainstem, which facilitate the transition from inspiration to expiration. Using structurally distinct M1 PAMs, we show that efficacy is target-mediated, but favorable cholinergic safety profiles are linked to the absence of allosteric agonist activity. Finally, we demonstrate that several common MeCP2 mutations are not associated with decreased M1 expression in autopsy samples and that M1 PAM efficacy is lost in representative mouse models of those mutations; potentially suggesting a need for a precision medicine approach in RTT.

T26. A Dopamine-Dependent Decrease in Dorsomedial Striatum Direct Pathway Neuronal Activity is Required for Learned Motor Coordination

Stefano Cataldi, Clay Lacefield, Shashaank N, Gautam Kumar, David Sulzer*

It has been suggested that the dorsomedial striatum (DMS) facilitates the early stages of motor learning for goal-directed actions, whereas at later stages, control is transferred to the dorsolateral striatum (DLS), which enables the motor actions to become a skill or habit. It is unknown whether these striatal regions are simultaneously active while expertise is acquired during skill learning. To address this question, we developed the mouse “treadmill training task” to track changes in mouse locomotor coordination during practice at running that simultaneously provides a means to measure local neuronal activity using photometry. We analyzed body position and paw movement to evaluate changes in motor coordination over practice sessions on the treadmill using DeepLabCut and custom-built code. By correlating improvements in motor coordination during training with simultaneous neuronal calcium activity in the striatum, we found that DMS direct pathway neurons exhibited decreased activity as the mouse gains proficiency at running. In contrast, direct pathway activity in the DLS was similar throughout training and did not correlate with learned skill proficiency. Pharmacological blockade of D1 dopamine receptors in these subregions during task performance confirmed that dopamine neurotransmission in the DMS direct pathway activity is necessary for efficient motor

coordination learning, while dopamine signalling in the DLS is important for both coordination learning and maintenance of the acquired skill. These results provide new tools to measure changes in fine motor skills during simultaneous recordings of brain activity, revealing fundamental features of the neuronal substrates of motor learning.

T27. Brainwide Mechanisms for Postingestive Learning

Christopher Zimmerman, Bichan Wu, Alejandro Pan-Vazquez, Emma Keppler, Brenna McMannon, Austin Hoag, Adrian Bondy, Ilana Witten*

Animals learn the value of foods based on their postingestive effects, and thereby develop preferences for foods that are nutrient-rich and aversions towards those that produce illness. However, it remains unclear how the brain tags individual flavors in a meal for learning, and further how tagged flavors are later associated with postingestive signals that arise after a delay of minutes or hours. Here we leverage the fact that mice learn to associate novel—but not familiar—foods with gastric malaise signals to investigate what distinguishes the neural representations of flavors that are tagged for learning versus those that are not. We first compared brainwide expression of the immediate early gene Fos across postingestive learning by using light sheet microscopy and machine learning tools to map the location of tens of millions of activated neurons. We discovered that flavor novelty produces distinct brainwide activation patterns during ingestion, malaise, and memory retrieval, and that >40% of brain regions are modulated during learning. We uncovered separate networks of modulated regions that are engaged in a learning-dependent manner during ingestion and during malaise. First, we found that taste and olfactory cortices (including piriform cortex) are preferentially active when mice consume novel flavors, whereas a set of limbic structures (including the septum) is engaged when mice consume safe, familiar flavors. We then artificially blocked these endogenous activity patterns to confirm that the piriform cortex and septum are critical for tagging novel flavors for learning. Second, we found that several amgydala subregions are activated by novel flavors and that this activation is later amplified during gastric malaise. We are now using in vivo recordings to test the hypothesis that reactivation of novel flavor-encoding amygdala ensembles supports postingestive learning, and that these reactivations are inhibited by septal activity when flavors are familiar.

T28. Differentiating Orbitofrontal Cortex Cell Populations Involved in Actions and Habits

Sophie Yount, Dan Li, Shannon Gourley*

The orbitofrontal cortex (OFC) is a large frontal cortical brain region thought to build so-called “task spaces,” a catalog of information necessary to develop strategies to obtain desired outcomes. As such, OFC activity is essential for goal-directed decision making (i.e., making a choice based on changes in outcome expectation). Meanwhile, hyper-activation of the OFC is also associated with habitual and compulsive-like behavior. How can the OFC support goal-directed action in some circumstances, but trigger habitual behavior in others? We tested whether distinct neuron populations in the OFC control goal-directed vs. habitual behavior. We used Fos-Targeted Recombination in Active Populations (TRAP) mutant mice to gain genetic access to neuron ensembles active following instrumental response training schedules that induce either goal-directed or habitual behavior. Then, we chemogenetically silenced each neuron population to determine its necessity in executing the counter behavior. Silencing OFC neurons active during the encoding of new reward information disrupted the execution of goal-directed behavior, as expected based on prior discoveries, and had no effect on the later execution of habitual behavior. Alternatively, silencing OFC neurons active after routine behavior had no effect on the expression of habitual behavior or later development of goal-directed behavior. Considering these results, we further interrogated the role of OFC neuron ensembles controlling goal-directed action. Stimulatory constructs were expressed in OFC neuron ensembles active after the encoding of new reward information. Later, we chemogenetically activated this neuron ensemble in order to overcome training schedules that typically induce habitual response strategies. Taken together, these results further suggest that a dissociable OFC neuron population necessary for the execution of goal-directed behavior exists, but there is no evidence of an existing neuron population necessary for the execution of habitual behavior within the OFC. Functionally defining OFC neuron populations will advance our understanding the region’s contribution to goal-directed action and improve future efforts to mitigate harmful habitual behaviors.

T29. Targeting A3 Adenosine Receptor (A3AR) Attenuates Paclitaxel-Induced Cognitive Impairment

Silvia Squillace, Michael Niehoff, Timothy Doyle, Susan Farr, Daniela Salvemini*

Paclitaxel, standard-of-care first-line chemotherapy for epithelial ovarian cancer and triple negative breast cancer, was shown to impair learning and memory functions in >50% of cancer survivors. Underpinning mechanisms of this major neurotoxicity are still mostly unknown, and there are no FDA-approved interventions. We developed a mouse model of paclitaxel-induced cognitive impairment whose cumulative dose is comparable to the total dose per cycle used in breast cancer patients. Paclitaxel-treated mice showed significant cognitive impairment in different hippocampal tests (T-maze, Novel Object Place Recognition test, NOPRT). Learning and memory functions were improved by co-administration of the selective A3 adenosine receptor (A3AR) agonist, MRS5980, without adversely affecting anxiety-like behavior and locomotor activity. Noteworthy, A3AR agonists possess anticancer activity and enhance the antitumor effects of paclitaxel. We previously shown that targeting A3AR successfully improved neurocognitive functions after cisplatin, another widely used chemotherapeutic. Collectively, the A3AR is emerging as an exciting novel approach in the treatment of a major chemotherapy-induced neurotoxicity. Keywords: Chemotherapy-induced cognitive impairment; A3 Adenosine receptor (A3AR); hippocampus; Paclitaxel; MRS5980.

T30. Hormonal Control of Dopamine and Reinforcement Learning

Carla Golden, Daljit Kar Grewal, Andrew Mah, Takashi Yamaguchi, Dayu Lin, Christine Constantinople*

A major outstanding question is how global physiological states influence neural dynamics and behavior. Here, we leverage endogenous fluctuations of gonadal hormones over female rats' reproductive cycles (estrous) as a natural entry point for relating quantifiable changes in global physiology to neural mechanisms of decision-making. We trained rats on a temporal wagering task, and found that their willingness to initiate trials is governed by a model-free learning algorithm that depends on the difference between received and expected rewards, which is referred to as the "reward prediction error" (RPE) in the theoretical framework of reinforcement learning. Dopamine release in the nucleus accumbens core (NAcc) encodes RPEs and is necessary

and sufficient for learning. We manipulated reward expectations by varying the magnitudes of offered rewards in blocks of trials. During the proestrus and estrus stages of the estrous cycle, when estradiol and progesterone are high, motivation varied more strongly with reward expectations. We identified a reduction in novel molecular targets of hormonal regulation involved in dopamine reuptake in the NAcc (including dopamine transporter) with mass spectrometry in proestrus and estrus and a reduction in dopamine transporter located at the synapse, where it needs to be to reuptake dopamine, with electron microscopy. This suggests that gonadal hormones enhance extracellular dopamine levels by reducing reuptake. Using fiber photometry of GRABDA to measure dopamine release, we found enhanced RPEs, providing a potential mechanism for how gonadal hormones promote learning. Current studies aim to probe the causal role of estradiol, specifically, on dopaminergic signaling during reward learning. This work reveals the mechanisms of hormonal modulation of dopamine at the behavioral, systems, circuit, and molecular levels.

T31. Dopaminergic Contributions to Evaluation and Reevaluation During Neuroeconomic Decision Making

Adrina Kocharian, David Redish, Patrick Rothwell*

Dopamine signaling in the nucleus accumbens core (NAc core) is an important neural substrate for neuroeconomic decision making. Dopamine dynamics reflect reward value, prediction error, and motivation, but have not been studied extensively under conditions of neuroeconomic foraging tasks known to show cognitive consideration of future and past events. Furthermore, decreases in dopamine have been seen in conditions of noxious stimuli or exogenous disappointment, but the dopamine dynamics in settings of internally-driven decision reevaluation are unknown. Using fiber photometry to monitor dopamine dynamics in mice during a neuroeconomic foraging task , we investigated how dopamine encodes evaluation and reevaluation of decisions. Mice were given a daily budget of one hour to forage for food rewards of four distinct flavors (restaurants). Upon entering a restaurant, mice first encountered an Offer Zone (OZ) in which a tone sounded, signaling the delay before reward would be delivered (higher pitched tones signaled longer delays, lower pitched tones signaled shorter delays). After the tone presentation in the OZ, the animal could either accept or reject the offer. Mice could reject the offer by continuing to the

next corner to receive an offer for a different flavored pellet. Mice could accept the offer by advancing into a Wait Zone (WZ), where the countdown to reward began. During the countdown, the animal had the opportunity to quit the trial at any point and only earned reward if it waited out the entire delay. Early in training, mice indiscriminately accepted most offers. As mice learned to budget their time, they increased their earnings by becoming more selective, rejecting offers for longer delays. The proportion of rewarded trials among accepted offers increased, as mice gradually reduced their quitting behaviors mid-countdown. The time invested before quitting also declined with training. Dopamine dynamics in the OZ scaled with the value of the offer. Accepting and rejecting offers were associated with opposing changes in dopamine. During training, when mice initially accept low-value offers, and quit the trial mid-countdown in the WZ, we observed decreases in dopamine preceding the quit, which may represent a reevaluation of the past or consideration of the future.

T32. Spatially and Temporally Selective Dynamics of Striatum-Wide Dopamine Release to Conditioned and Unconditioned Stimuli and Rewards

Mai-Anh Vu, Michelle Wen, Eleanor Brown, Lydia Mroz, Timothy Otchy, David Boas, Mark Howe*

Dopamine release in the striatum is critical for diverse functions, including motivation, reward response, motor control, learning, and memory. Recent studies have provided evidence that dopamine release to cues, rewards, and movements varies in amplitude and timing across striatal sub-regions, suggesting that region-specific dopamine signals may support distinct functions in learning and behavior. Current optical approaches have been limited to measuring dopamine release across only one or two small striatum regions in a given subject. Thus, a complete view of the spatiotemporal evolution of rapid dopamine signals during learning and behavior throughout the striatum is lacking. To address this, we have developed a multi-fiber photometry approach to monitor dopamine release with sub-millimeter spatial resolution at over 50 locations simultaneously throughout the striatum in awake, behaving mice expressing the fluorescent dopamine indicator dLight 1.3. Our chronic implants allow us to record stable signal for months, enabling me to track changes in dopamine release on timescales ranging from 10s of milliseconds to weeks, as mice were presented with salient stimuli and

then were trained in a Pavlovian learning task. My data provide evidence for spatial variations across 3 dimensions in dopamine release to conditioned and unconditioned stimuli and rewards, and in the dynamics of the cue- and reward-related signals across Pavlovian learning at multiple timescales. Taken together, these initial findings provide the largest scale description of rapid dopamine release topography in the striatum to date and define the spatial territories over which functional dopamine signals may influence distinct aspects of learning and behavior.

T33. Developmental Changes in Medial Prefrontal Cortex Circuitry Contribute to Reduced Adaptive Avoidance Behavior in Adolescent Mice

Caitlin Goodpaster, Laura DeNardo, Cassandra Klune, Nico Jones, Rita Chen*

The medial prefrontal cortex (mPFC) and its connecting circuitry play an essential role in the development and execution of many adaptive behaviors, including decision making. The mPFC undergoes protracted development, not reaching maturity until early adulthood. Thus, it is thought that experiences in early life, especially in the adolescent period, help shape the development of the mPFC to produced nuanced and adaptive behavioral responses later in life. Yet, it is poorly understood when specific mPFC circuits mature and how they differentially regulate behavior across development. To fill this gap our lab utilizes a platform mediated avoidance (PMA) assay where a fear conditioned tone prompts mice to navigate to a safety platform. Successful avoidance in this behavior in adults has been shown to be bidirectionally controlled by two mPFC projections—those to the nucleus accumbens (NAc) and the basolateral amygdala (BLA). Our lab has found that both adolescent and adult mice are able to successfully learn to move to the platform to avoid the shock in one training day. Interestingly, while adults display high levels of avoidance during a retrieval session 24 hours later, adolescent mice do not – indicating possible differences in behavioral strategy or retention deficits. Optogenetic manipulations of both mPFC NAc and mPFC BLA pathways during PMA produced distinct behavioral changes during adolescence when compared to adulthood. Additionally, fiber photometry recordings indicate that NAc and BLA show differential response dynamics during PMA between the two ages. These findings suggest that mPFC projections to NAc and BLA are differentially active in adolescence, leading to reduced avoidance behavior seen at this age. Ultimately, elucidating how mPFC

circuitry matures across development is needed to better understand how perturbations in early life can lead to mental illnesses, such as anxiety and depression, that are characterized by excessive avoidance.

T34. Insular-Prefrontal Circuit Driving Compassionate Social Behavior

Songjun Li, Pauline Gabrieli, Moeko Suzuki, Omer Zeliger, Jack Demaree, Renee Cauchon, Nicole Occidental, Ziv Williams*

Compassionate behavior, or the ability to help others in need, is a cornerstone of prosocial interactions. To benefit others, it is necessary for individuals not only to perceive the internal states or emotions of others but also to take appropriate actions. Yet, how mammalian neurons precisely link social-specific information with adaptive behavior has been a major challenge to understand. Here, we developed a place-preference assay that allowed mice to directly control in real-time the experience of a nearby conspecific partner while also allowing the animal's own actions to be dissociated from the other's identity. Behaviorally, we found that wild-type male mice consistently chose to reduce aversive experiences of familiar but not unfamiliar partners, actions not observed when visual and olfactory cues were blocked. By recording from anterior insular (AI) neurons, we identified cells that encoded task relevant information, including the social identity of the animal's partners and their specific experience. Dorsal anterior cingulate (dACC) neurons, by contrast, preferentially encoded information about the act of helping their partners, displaying changes in activity prior to making their decisions. Further, whereas information about the experience of others could be predominantly decoded from AI activity, information about the animal's prosocial actions could be predominantly decoded from dACC activity; demonstrating a partitioning of information within the insular-prefrontal circuit. Finally, chemogenetic excitation of AI-to-dACC projectors but not dACC-to-AI projections increased compassionate behavior while inhibitions of both dACC to AI as well as AI to dACC projectors, on the other hand, decreased this behavior with familiar partners. Taken together, these findings identify a putative insular-prefrontal circuit for driving compassionate behavior and a mechanism that could allow insular neurons to instruct social-specific actions through prefrontal control.

T35. Transcription Factor 4 Coordinates Developmental and Dopamine-Related Transcriptional Signatures in the Striatum

Nathaniel Robinson, Jenna Hinds, Saige Thompson, Brooke Walker, Jeremy Day*

The striatum subserves myriad roles in motor learning, executive function, and motivated behaviors. At a molecular level, striatal development is governed by coordinated epigenetic programs that are orchestrated by master transcription factors (TFs), particularly in medium spiny neurons (MSNs). Notably, a host of neurodevelopmental disorders are caused by mutations in these TFs and are characterized by delayed motor development coupled with cognitive and behavioral dysfunction, thus implicating the striatum in the pathophysiology of these disorders. Pitt-Hopkins syndrome (PTHS), which is caused by loss-of-function mutations in the neuronal master TF, transcription factor 4 (TCF4), manifests as a constellation of motor and behavioral symptoms. However, the extent to which striatal neurodevelopment is disrupted in PTHS remains poorly understood. Using an innovative dual CRISPR activation/interference strategy paired with gene expression and chromatin accessibility profiling, we have discovered a previously unknown function for TCF4 in regulating gene networks governing neurogenesis, cell type specification, and neuroplasticity in MSNs, accompanied by widespread chromatin remodeling and the recruitment of key neurodevelopmental TFs. Moreover, differential TCF4 expression patterns are visible across distinct stages of human striatal development and MSN differentiation. Mechanistically, TCF4 controls the distribution of D1- versus D2-MSNs and choreographs their global transcriptional and electrophysiological responses to dopamine, a critical mediator of the motor and behavioral outputs of the striatum. Our results reveal TCF4 as an essential regulator of the molecular events that define MSN development and neuromodulation. These findings expand our fundamental understanding of neurodevelopment and provide a foundation for examining the contributions of TCF4-driven epigenetic programs in the striatum to neurodevelopmental disease.

T36. The Nanoscale Organization of Inhibitory Synapses Throughout the Somato-Dendritic Axis

Joshua Garcia, Katharine Smith, Kevin Crosby, Sara Gookin, Amber Truit, Samantha Schwartz*

Inhibitory synaptic transmission is essential for maintaining proper neuronal excitability in the brain. GABAergic synapses dampen neuronal activity, control excitatory synaptic plasticity, and synchronize circuits through the shaping of neuronal output. Based on molecular composition and function, there is vast GABAergic synaptic diversity across neuronal subcellular compartments. Inhibitory synapses formed along the somato-dendritic axis receive input from distinct interneuron subtypes, and exhibit very different functions. Synapses formed on the soma synchronize circuits through sculpting neuronal output and spike timing, whereas those that innervate dendrites control excitatory activity and dendritic integration. However, our fundamental understanding of the molecular and structural diversity between these synaptic sites remains unknown. Our recent work has shown that inhibitory synapses exhibit a nanoscale organizational principle, similar to that of glutamatergic synapses. This common nanoscale subsynaptic organization is thought to be crucial for synapse function and plasticity, and in the case of inhibitory synapses, may contribute to their unique and striking diversity of function. Here we investigate this diversity using super-resolution microscopy methods to interrogate the nanoscale organization of different inhibitory synapse subtypes. We show differential nanoscale organization of postsynaptic GABAARs and their scaffold, gephyrin, throughout the somato-dendritic axis. Somatic synapses were consistently larger than dendritic synapses, with larger post-synaptic domains, higher numbers of GABAARs and larger active zones. Somatic synapses were also structurally more complex compared with their dendritic counterparts: they exhibited more intricate nanoscale organization of GABAARs and gephyrin. Together, our data suggest that nanoscale organization of inhibitory synapses could be a key driver underlying the diversity of synaptic inhibition.

T37. Synaptic Scale Dopamine Disruption in Huntington's Disease Model Mice Imaged With Near Infrared Catecholamine Nanosensors

Sarah Yang, David Schaffer, Markita Landry*

Dopamine (DA) neuromodulation is a foundational signaling process in the brain that facilitates learning, motivation, and motor control.

Disruption of dopamine signaling is implicated in several neurological and psychiatric disorders including the neurodegenerative motor disorder Huntington's Disease (HD). Despite established clinical relationships between HD and dopamine, the exact mechanisms of disease development and progression are not fully understood. In contrast to classical neurotransmitter signaling, dopamine can signal across defined synapses as well as diffuse far from release sites to influence the excitability of multiple neighboring neurons. As such, developing tools that enable visualization of dopamine release at the spatio-temporal resolution of single release sites (µm, ms) is critical to not only understanding how dopamine operates in health and disease but also how to best develop novel therapies (RNAi, cell replacement). To this end, we employ near-infrared fluorescent catecholamine nanosensors (nIRCats) to image dopamine release within the brain striatum of R6/2 Huntington's Disease Model (R6/2) mice. We develop a set of metrics and methods to characterize spatial changes in dopamine release from nIRCat recordings early and late in disease. Analysis of nIRCat imaging using these metrics reveals that dopamine disruption in late HD is primarily driven by decreased dopamine releasing sites (dopamine hotspots) combined with a moderate decrease in release site performance (mean peak dF/F). We also track single nIRCat imaged dopamine release sites over multiple stimulations and demonstrate late HD dopamine depletion is further compounded by temporal disruptions in dopamine release (release fidelity). Lastly, we interrogate this late HD state by examining external calcium sensitivity and utilizing nIRCats' dopamine pharmacology compatibility to assess changes in Dopamine D2 Receptors (D2R) expression. These studies reveal spatial disruptions in dopamine release previously undetected by spatially diffuse dopamine sensors and underscore the utility of nIRCat as a versatile new tool for visualizing dopamine release during neurodegeneration.

T38. Parkinson's Risk Gene, Synaptojanin1, Regulates Dopamine Transporter Trafficking

Jacqueline Saenz, Pingyue Pan*

Parkinson's disease (PD) is a prominent neurodegenerative disease in the aging population characterized by the deterioration of dopaminergic neurons in the substation nigra. Mutations of SYNJ1 (synaptojanin1/Synj1) are linked to families with Parkinsonism. Recent studies from our lab and others have shown that Synj1 deficiency in mice led to dopamine neuron-

specific synaptic defects such as impaired synaptic vesicle endocytosis and abnormal dopamine transporter (DAT) clusters. To determine that Synj1 regulates DAT trafficking and to identify the molecular underpinnings of this regulation we used multiple imaging strategies. Our data showed that in the striatum of aged Synj1+/- mice DAT immunofluorescence was increased. Similarly, DAT was increased in the soma and axons of cultured Synj1+/- dopamine neurons. However, using a combination of antibody staining, fluorescent DAT ligand, JHC1-64, and expressing our recently engineered DAT reporter, DAT-pHluorin, we show that the steady state surface DAT (sDAT) was reduced in Synj1+/- neurons. Consistently, in N2a cells expressing human SYNJ1 harboring PD mutations, we find significantly decreased sDAT expression compared to the control non-transfected cells and wild type SYNJ1 transfected cells, indicating that Synj1 deficiencies impair the maintenance of sDAT. Furthermore, pharmacological reagents that increase PI(4,5)P2, a major enzymatic substrate of Synj1, mimics Synj1 deficiency in reducing sDAT fraction, suggesting possible regulation of sDAT expression by PI(4,5)P2 signaling pathways. Future studies will be aimed at exploring the PI(4,5)P2 downstream PLCδ-PKCβ pathway in facilitating DAT internalization and dissect the endocytic routes of DAT using gene knockdown strategies in wild type and Synj1-deficient neurons.

T39. Locus Coeruleus-Driven BOLD Global Signal Changes in Alzheimer's Rat Model

Nmachi Anumba, Michael Kelberman, Corrie Smith, Wen Ju Pan, Nan Xu, Alexia Marriott, Ellen Kim, David Weinshenker, Shella Keilholz*

Background: Functional connectivity of the brain as measured by the blood oxygen level dependent (BOLD) signal in fMRI is altered during Alzheimer’s disease (AD) progression. Common practice during preprocessing of fMRI data is removal of the global signal, defined as the averaged brain signal, removing major sources of noise while risking loss of neural activity. The locus coeruleus (LC), one of the first brain regions to accumulate hyperphosphorylated tau, contributes to brain-wide neuromodulatory regulation. We combined optogenetics and fMRI to study how LC activity affects the global signal in the TgF344-AD rat model of AD, which overexpresses mutant human amyloid precursor protein and presenilin-1.
Methods: At 2 months of age, TgF344-AD rats and WT littermates received intra-LC infusions of a ChR2-mCherry virus under the

noradrenergic specific PRSx8 promoter. 2-4 weeks prior to fMRI, rats were implanted with an optic ferrule targeting the LC. Functional ChR2 expression and LC activation were confirmed by pupil dilation following optogenetic LC stimulation. At ~6 months of age, rats underwent 10-minute fMRI scans at baseline and 5 Hz optogenetic stimulation. Rats were anesthetized with 1.3% isoflurane, intubated, and administered pancuronium (1.5 mg/kg*hr, s.c.). fMRI scans were gradient echo EPI (TR = 1.25 s) and obtained using a 9.4T Bruker Animal MRI scanner. Data were preprocessed using a customized pipeline. The analysis was performed by correlating each voxel timecourse with the global signal via Pearson's linear correlation.
Results: Wildtype animals showed an increased correlation to the global signal along the midline and in bilateral cortical areas. This correlation increased under 5 Hz LC stimulation. AD rats had lower levels of correlation but also saw an increase in global signal correlation from the same structures with LC stimulation. This indicates that global signal removal, especially under LC-driven brain states, could eliminate neural data.

T40. Projection-Specific Regulation of Nigrostriatal Dopamine by the Subthalamic Nucleus

Nick Hollon, Lotfi Hadjas, Grace Kollman, John Hiedo, Thomas Hnasko*

Nigrostriatal dopamine (DA) and the subthalamic nucleus (STN) are key substrates of Parkinson's disease (PD) pathology and treatment, but their interactions remain poorly understood. Here we investigated how STN projections to the substantia nigra regulate DA neuron activity. We injected dual-recombinase mice (VGLUT2-Cre x DAT-Flpo) with AAVs to express Cre-dependent ChrimsonR in the STN and Flp-dependent GCaMP6f in substantia nigra pars compacta (SNc) DA neurons. Brief optogenetic stimulation of STN terminals in the nigra increased DA neuron GCaMP signals. Prolonged high-frequency stimulation revealed multiphasic DA neuron responses: Transient excitation transitioned to sustained inhibition for the duration of the stimulation, with rebound excitation at stimulation offset. Recording GABA neurons in the substantia nigra pars reticulata (SNr) instead revealed sustained excitation throughout stimulation. DA axons in separate striatal subregions exhibited distinct responses to STN terminal stimulation: DA axons in the tail of the striatum were transiently activated at stimulation onset, whereas those in more rostral dorsolateral striatum were inhibited

during stimulation and had prominent rebound excitation, and central dorsal striatum responses were more heterogeneous.
These results are consistent with hypothesized circuitry entailing modest direct excitatory input from STN to SNc, with disynaptic inhibition mediated by canonically dense STN projections to SNr. Distinct activity of DA axons in separate striatal subregions suggests that STN and likely SNr may differentially regulate DA neuron subpopulations in the dorsal and ventral tiers and lateral SNc, which give rise to these topographically organized nigrostriatal projections. As SNc DA subtypes exhibit differential vulnerability in PD, important future work will investigate STN regulation of spared DA neurons following selective ablations of preferentially vulnerable DA subtypes.

T41. A Prefrontal to Midbrain Periaqueductal Gray Circuit Restrains Passive Coping Stress Response Patterns

Timothy Skog, Terry Beltz, Jordan Luna, Shane Johnson, Dalton Hinz, Ryan Lingg, Sara Romig-Martin, Alan K Johnson, Jason Radley*

Disturbances in medial prefrontal cortex (mPFC) function are believed to play an important role in the shift from adaptive to maladaptive responses to environmental threats, however the mechanisms underlying these phenomena are not well understood. The midbrain periaqueductal gray (PAG) coordinates defensive behavioral with autonomic response features. That PAG receives dense input from the mPFC raises the prospect for higher-order control in the modulation of defensive behaviors. Here we utilized optogenetics to investigate the functional role of the rostral prelimbic mPFC– ventrolateral PAG pathway in coordinating coping responses to an aversive stimulus. The projection from the rostral prelimbic mPFC-to-ventrolateral PAG was transfected with an adeno-associated virus (AAV) expressing a Cre-inducible, light-sensitive chloride pump halorhodopsin, cation channel channelrhodopsin, or fluorescent reporter only. A Cre-containing, retrogradely transported, AAV was injected in ventrolateral PAG to induce opsin expression in PAG-projector neurons in rostral prelimbic mPFC. Using the shock probe defensive burying test to measure active (defensive burying) and passive (immobility) coping behaviors in response to a noxious shock, we found that inactivation significantly increased the time male and female rats spent immobile (by 65%, $p<.05$) and produced a downward trend in defensive burying of the probe ($p=.07$), while photoactivation attenuated immobility ($p<.05$) without

affecting burying. Inhibition of this pathway concurrently prevented the increase in arterial blood pressure ($p<.001$) and heart rate ($p<.01$) provoked by the shock. These data reinforce previous work implicating the ventrolateral PAG as a neural hub for coordinating passive behavioral with bradycardiac/ depressor features of a passive coping set and that this response may be subject to top-down intervention from the mPFC. These results may provide a framework for conceptualizing how prefrontal dysfunction may induce maladaptive shifts typified by exaggerated passive avoidance and elevated autonomic activation.

T42. Neural Basis of Collective Response to Cold Stress in Social Groups

Tara Raam, Linfan Gu, Qin Li, Naren Ramesh, Stephanie Correa, Weizhe Hong*

Social interactions are critical to the well-being of a wide variety of species. While a growing body of literature has identified neural circuits for dyadic social interactions, our understanding of higher order interactions at the group level is weak. Many species organize into social groups, in which the individual contributes to and benefits from the well-being of the whole. However, little is known about the neural basis of group behaviors in response to environmental stressors. To address this gap, we are using a novel approach to study how groups of mice self-organize into huddles in response to thermal cold stress. Here, we used computer-vision based multi-animal pose estimation tools to identify five unique huddling states in groups of four mice. We found that huddling behavior is modulated by group size--individual mice huddle more in groups than in pairs, suggesting that social groups have emergent properties that dyads do not have. Moreover, we found that groups adapt their huddle states according to the degree of the ambient temperature, and that huddle states dynamically evolve throughout a session. We then asked which neural circuits coordinate huddling in response to cold stress. Previous work suggests that medial prefrontal cortex (mPFC) is a critical node for regulating dyadic and group level social behaviors. Using Miniscope calcium imaging, we found a unique population of cells in mPFC that encode decisions to engage or disengage from a huddle, but do not encode other social behaviors. Using mPFC population activity, we found that huddling behaviors are separable from other behaviors in population space, and can be accurately decoded from other behaviors using SVM classifiers. We also found that mPFC neurons encode the social identity of huddling partners. Together, these data suggest a

critical role for mPFC in encoding group-level responses to stress and present a novel avenue towards studying social interactions in larger groups.

T43. Electrochemical-Based Aptamer Sensors for the Real-Time Monitoring of Various Drugs in Brain

Nicole Emmons, Julian Gerson, Tod Kippin, Kevin Plaxco*

The temporal resolution with which we can measure the distribution of drugs into the brain is orders of magnitude too slow to capture the concentrations associated with altered physiological/therapeutic processes. EAB (electrochemical-based aptamer) sensors, a biomimetic, aptamer-based biosensor sensor platform, have been demonstrated to support the seconds-resolved, real-time measurement of a wide range of molecular targets in situ in the veins and brain tissue of living subjects. Our sensors have been functionalized to detect varying classes of drugs, including psychoactive drugs, chemotherapeutics, and antibiotics. We tested this new technology in rats intravenously dosed with drug targets of interest while measuring target concentrations using an EAB sensor placed in the brain with concurrent locomotor monitoring. We successfully measured procaine concentrations every ~10 s in real-time and generated subject-specific pharmacokinetic profiles that are compared to the pharmacodynamic (behavioral) response to generate in-brain concentration-behavior profiles for each subject. We further developed a Feedback-Controlled automated drug delivery system capable of maintaining drug levels constant at desired concentrations allowing for experimentally controlled individualized pharmacokinetics. Additionally, we have optimized our sensor for the chemotherapeutic, doxorubicin, to detect molecular concentrations of the drug in the brain. Importantly, we have used our EAB against doxorubicin (which does not cross the BBB) to verify a lack of accumulation in the brain indicating in-brain EAB placement does not disrupt physiological regulatory processes. We are currently using this approach to assess strategies aimed at facilitating the delivery of this drug into brain tissue (ex: liposomal glutathione). This quantification will not only inform whether brain concentrations reach levels sufficient for the treatment of intracranial cancers but may also elucidate mechanisms underlying chemotherapy-induced cognitive deficits. We have developed a novel, revolutionary, technology that can measure the pharmacokinetics of many classes of drugs within the brains of awake, freely behaving animals and can be used to both track and control precise drug concentration in real-time.

T44. Unraveling the Complex Effects of Inflammatory Injury on Nociceptive Processing in Spino-Periaqueductal Gray Neural Circuits

Chelsie Brewer, Julie A. Kauer*

Modeling inflammatory injury via high-intensity stimulation of peripheral nerves at low frequencies (LFS) potentiates excitatory drive to spinal neurons projecting (PNs) to the midbrain periaqueductal gray (PAG), a hub for pain processing. We sought to identify the afferent population driving this potentiation and downstream effects on spino-PAG PN output to supraspinal pain circuits. We used 3 to 6-week-old mixed-sex mice. In spinal experiments, we used mice expressing channelrhodopsin (ChR2) driven by TRPV1 gene expression (to stimulate C fibers) and back-labeled spino-PNs from the PAG using dil. We recorded from spino-PAG PNs in a semi-intact spinal cord preparation using whole-cell patch-clamp. Inflammation increases C fiber firing rates to 1-2 Hz; therefore, we used LFS (1–5 ms, 470 nm LED pulses at 2 Hz for 2 mins) to model inflammatory injury. Stimulation of TRPV1-expressing (TRPV1+) peripheral afferents induced burst firing in most spino-PAG PNs sampled. LFS persistently (≥20 min) increased the number of APs within each C fiber-induced burst (n=10, p=0.029) and relied on postsynaptic G proteins, NMDA receptors, and presynaptic TRPV1+ fibers. Also, LFS may increase the intrinsic excitability of spino-PAG PNs— by decreasing AP threshold (n=14, p=0.015) and increasing membrane resistance (n=14, p=0.0003). Taken together, this suggests that TRPV1+ fiber LFS persistently increases spino-PAG PN output. In supraspinal experiments, we prepared acute PAG slices from mice expressing ChR2 in all ascending spinal terminals. Our preliminary data suggest that spinal axons synapse onto μ opioid receptor-expressing neurons in the PAG—and LFS induces long-term depression in unidentified PAG neurons. We are now investigating burst firing in spinal afferents in the PAG and analyzing the population-level dynamics of these circuits using calcium imaging.

T45. Neuropathic Pain as a Trigger for Histone Modifications in Limbic Circuitry

Svetlana Bryant, Julie-Anne Balouek, Luke Geiger, David Barker, Catherine Peña*

Chronic pain involves both central and peripheral neuronal plasticity that encompasses changes in the brain, spinal cord, and peripheral nociceptors. Within the forebrain, mesocorticolimbic regions associated

with emotional regulation have recently been shown to exhibit lasting gene expression changes in models of chronic pain. To better understand how such enduring transcriptional changes might be regulated within brain structures associated with processing of pain or affect, we examined epigenetic modifications involved with active or permissive transcriptional states (histone H3 lysine 4 mono and trimethylation, and histone H3 lysine 27 acetylation) in periaqueductal gray (PAG), lateral hypothalamus (LH), nucleus accumbens (NAc), and ventral tegmental area (VTA) 5 weeks after sciatic nerve injury in mice to model chronic pain. For both male and female mice in chronic pain, we observed an overall trend for a reduction of these epigenetic markers in periaqueductal gray, LH, and NAc, but not VTA. Moreover, we discovered that some epigenetic modifications exhibited changes associated with pain history, while others were associated with individual differences in pain sensitivity. When taken together, these results suggest that nerve injury leads to chronic chromatin-mediated suppression of transcription in key limbic brain structures and circuits, which may underlie enduring changes in pain processing and sensitivity within these systems.

T46. Sex Differences in Shock-Elicited Neural Activity in Pain and Fear Networks

Julia Mitchell, Mikaela Laine, Leena Ziane, MaryClare Pikus, Emmett Bergeron, Jack Keith, Akshara Kannan, Roberto Calitri, Rose Clark, Rebecca Shansky*

A key component of auditory cued fear conditioning is the unconditioned stimulus (US), often an aversive foot shock. Individual differences in how an animal experiences the aversive foot shock could affect behavior during Pavlovian fear conditioning due to differences in pain sensitivity. In this study we investigated the relationship between individual differences in pain sensitivity and behavior during Pavlovian fear conditioning in male and female rats. To assess pain sensitivity, we measured latency to paw withdrawal in the hot plate test. Four days later, animals went through auditory cued fear conditioning where an auditory tone was paired with a low intensity shock, high intensity shock, or no shock. Ninety minutes following fear conditioning, animals were perfused and both brains and spinal cords were dissected and stained for cFos+ cells. We focused on areas involved in conditioned fear responses, pain processing, or both: regions of the prefrontal cortex (PFC), amygdala, columns of the periaqueductal gray (PAG), and the dorsal

horn of the lumbar spine. We found significant correlations between latency to withdraw the hind paw in the hot plate test with both conditioned and unconditioned responses in 0.3 mA females only, although this was dependent on conditioned response. In our cFos data, we found main effects of location (on a rostral/caudal gradient) and shock intensity, dependent on sex in the brain regions. Sex differences were found in cFos+ expression in the caudal prelimbic, infralimbic cortex and spinal cord, only. Significant correlations between conditioned, unconditioned responses and cFos+ expression were found in the regions of the PFC, in females only. The results from this study suggest that there are sex differences in aversive stimuli processing, which can be reflected in both behavioral and neural outputs.

Saturday, January 21, 2023

OPENING PLENARY

8:00 AM – 9:30 AM • BALLROOMS 1, 2 & 3

Race and the Brain: Insights From the Neural Systems of Emotion and Decisions

Presenter: Elizabeth Phelps

Investigations of the neural systems mediating the processing of social groups defined by race, specifically Black and White race groups in American participants, reveals significant overlap with brain mechanisms involved in emotion. This talk will provide an overview of research on the neuroscience of race and emotion, focusing on implicit race attitudes. Implicit race attitudes are expressed without conscious effort and control, and contrast with explicit, conscious attitudes. In spite of sharp decline in the expression of explicit, negative attitudes towards outgroup race members over the last half century, negative implicit attitudes persist, even in the face of strong egalitarian goals and beliefs. Early research demonstrated that implicit, but not explicit, negative attitudes towards outgroup race members correlate with blood oxygenation level dependent signal in the amygdala – a region implicated in threat representations, as well as emotion's influence on cognition. Building on this initial finding, we demonstrate how learning and decisions may be modulated by implicit race attitudes and involve neural systems mediating emotion, learning and choice. Finally, we discuss techniques that may diminish the unintentional expression of negative, implicit race attitudes.

Saturday, January 21, 2023

PIONEER SESSION #1

9:15 AM - 11:15 AM • SUPERIOR

Treatment of Overdose in the Synthetic Opioid Era

Pioneer: Phil Skolnick
Chair: Amy Newman

Overdose deaths are often viewed as the leading edge of the opioid epidemic which has gripped the United States over the past two decades: opioid overdose is both the number-one cause of death for individuals between 25-64 years old and a significant contributor to the decline in average lifespan in the United States. Over the past 7-8 years, there has been a dramatic increase in the misuse of illicit synthetic opioids ("synthetics"), primarily fentanyl and related piperidine-based analogs. CDC estimates indicate there were over 80,000 opioid overdose deaths in 2021, with almost 90% linked to synthetics. By comparison, there were 34,000 opioid overdose deaths in 2015, with about 30% linked to synthetics. Multiple studies modeling trends in opioid misuse predict up to 1.2 million overdose deaths during the next decade. In this presentation, I will describe the "wave like" evolution of the opioid epidemic and discuss the unique physicochemical and pharmacological properties of synthetics which drive both the morbidity/mortality associated with their misuse as well as their widespread availability. In the face of a continued rise in opioid overdose deaths, the competitive μ opioid receptor antagonist naloxone remains the "gold standard" reversal agent. However, among the consequences resulting from the misuse of potent synthetics is the need for higher naloxone doses to reverse an overdose. The development of more effective reversal agents is an essential component of a tripartite strategy endorsed by both the NIH and The President's Commission on Combatting Drug Addiction and the Opioid Crisis to reduce the biopsychosocial impact of opioid misuse in the synthetic era. In this presentation, I will describe the development of nalmefene nasal spray, using this program to illustrate both the scientific and regulatory challenges in developing novel rescue agents to treat opioid overdose.

Saturday, January 21, 2023

PROFESSIONAL DEVELOPMENT SESSION #1

SPECIAL SESSION • 2:00 PM – 3:00 PM • MAGPIE B

Designing Science Presentations: Simple Design Strategies to Improve Scientific Talks, Posters, and Papers

Presenter: Matt Carter

What lessons can scientists learn from professional designers to improve their figures and talks? This professional development session will discuss simple design strategies that scientists can employ to greatly increase the impact of their presentations. During this session we will workshop some examples of figures and slides and discuss ways to increase their effect on an audience. By the end, attendees will learn some tangible skills and resources for designing better presentations regardless of their specific scientific fields.

SATURDAY AFTERNOON PANELS

PANEL • SATURDAY • 4:30 PM – 6:30 PM • BALLROOM I

Sex Differences in Brain Injury: Does It Matter?

Chairs: Cole Vonder Haar, Akiva Cohen

Presenters: Kristen Pechacek, Rachel Rowe, Olga Kokiko-Cochran, Akiva Cohen

Traumatic brain injury (TBI) is a major health concern, with over 2.8 million recorded annually in the US. TBI has a significant impact not only on financial aspects, but also on morbidity and disability in our healthcare system, and emerging evidence suggests pathology and recovery from TBI differs between the sexes. This panel will explore neural and inflammatory mechanisms underlying sex differences in TBI-related pathologies and recovery. Specifically, speakers will detail sex differences associated with functional impairments, alterations in neural signaling, and recovery trajectories in basic and translational research designs. Kristen Pechacek (Ohio State University) will focus on how

neuroinflammation modulates psychiatric symptoms such as impulsivity in rats and whether treatments targeted towards microglia are sufficient to overcome TBI-induced deficits. Rachel Rowe (University of Colorado Boulder) will detail data on sex differences in sleep-wake disturbances after TBI and discuss how sex-dependent immune-endocrine interactions may play a role in the pathophysiology of these sleep symptoms. Olga Kokiko-Cochran (Ohio State University) will discuss the role of microglia will discuss the influence of sex in the microglia response to post-injury stress. Specifically, she will describe unique stress-immune signaling in males and females after post-injury sleep fragmentation. Akiva Cohen (University of Pennsylvania) will present data on specific sex-dependent mechanisms underlying hypothalamic orexin neuron dysfunction that contributes to TBI-induced inability to maintain wakefulness. At the conclusion of these presentations, audience members will have an appreciation for sex-dependent differences in various TBI pathologies which could lead to sex-dependent therapies to treat TBI patients.

PANEL • SATURDAY • 4:30 PM – 6:30 PM • MAGPIE A

Mechanisms of Social Cognition: Insights From Neuroimaging, Computational Approaches and Psychopathology

Chair: Christina Carlisi

Presenters: Christina Carlisi, Dorit Kliemann, Caroline Charpentier, Tessa Rusch

As inherently social beings, social cognition and decision-making are essential to human life. They crucially influence our relationships, activities and wellbeing. It is well-established that atypical social cognition can lead or contribute to mental health problems and psychiatric conditions, from anxiety and depression to autism. However, the mechanisms of social cognition remain largely unknown. On top of that, the limited understanding we do have stems from research conducted through a specific cultural lens primarily in white, western countries, hindering the generalisability of our current knowledge. This panel will explore social cognition from multiple angles. We will provide an overview of different approaches across neuroimaging, computational and behavioural research on social processing, including neural network activation, computational models of decision-making, and behavioural characteristics of facial emotion perception. This collection of talks will synthesize a deeper understanding of social

cognition, providing the audience with new perspectives on how research can be applied across health and disease. Christina Carlisi (chair and panelist) will provide introductory comments and lead discussion of the presentations. She will open with an overview of neural mechanisms and cross-cultural biases in social perception, discussing the implications of how this relates to how we study and treat mental illness. Dorit Kliemann will discuss functional brain connectivity in autism, a disorder characterised by differences in social cognition, with a focus on reproducible research. Caroline Charpentier will discuss the computational basis of social learning, exploring how learning and decision-making in social contexts relates to variations along psychiatric symptom dimensions. Tessa Rusch will close the session with a discussion of computational characterizations of social inference, to examine how social inferences guide interactive behaviour.

PANEL • SATURDAY • 4:30 PM – 6:30 PM • MAGPIE B

What Immediate Early Genes Can Tell Us about Memory and Brain Plasticity

Chairs: Jason Shepherd, Christine Ann Denny
Presenters: Yingxi Lin, Ivo Spiegel, Anne West, Jason Shepherd

Activity-induced gene expression underlies experience-dependent plasticity and memory consolidation in the brain. The first rapid wave of genes induced, immediate early genes (IEGs), play key roles in these processes. However, most studies only use IEGs as proxy markers for circuits activated during various behaviors and less is known about their specific functions. In this panel, we will highlight new studies that shed light on the specific functions of IEGs in cells and circuits. These studies span epigenetic regulation of gene expression, to memory formation and processing of sensory information. The talks cover:
1. Onset of IEG induction during early development signifies activity-dependent neural circuit maturation (Yingxi Lin).
2. How IEGs and the enhancers of their target genes homeostatically maintain every day neural activity rates and the precision of sensory coding (Ivo Spiegel)
3. How modulating expression of specific IEGs, using dCas9-CRISPR epigenome editing, affects neuronal membrane properties (FOS) and may alter receptive field plasticity (Arc) in visual cortex (Anne West).
4. How the IEG Arc may mediate a novel intercellular form of synaptic plasticity to consolidate memory (Jason Shepherd).

PANEL • SATURDAY • 4:30 PM – 6:30 PM • PRIMROSE A

Prefrontal Cortical Regulation of Aversive Emotional Processing

Chair: Joshua Johansen, Roger Clem

Presenters: Laura DeNardo, Fabricio Do Monte, Roger Clem, Joshua Johansen

Aversive emotional experiences trigger coordinated behaviors and autonomic reactions that facilitate survival. Such experiences range from innately aversive events to those requiring evaluative processes such as memory retrieval, planning, conflict resolution and inference. Subcortical systems important in simple aversive associative learning have been studied extensively, but how higher order forms of emotional processing are controlled by the nervous system is not well understood. In this panel, speakers will focus on the role of the rodent medial prefrontal cortex (mPFC) in emotional learning, threat avoidance and inference. The first speaker, Laura DeNardo, will discuss studies examining prefrontal cortical control of threat avoidance across development, focusing on the in-vivo function of frontolimbic avoidance circuits at juvenile, adolescent and early adult stages. Next, Fabricio Do Monte will consider the function of the prelimbic subregion of the mPFC in risky decision-making with particular emphasis on the role of prelimbic projections to the paraventricular nucleus of the thalamus and the nucleus accumbens in approach-avoidance conflict. Roger Clem will then present work revealing discrete subpopulations of prefrontal GABAergic interneurons that regulate fear memories, and how they control brain networks underlying aversion and reward. Finally, Josh Johansen will discuss experiments investigating how mPFC neuronal populations encode an internal model of salient associations to enable emotional inference through projections to subcortical targets such as the amygdala. Together, these presentations will provide new insights into prefrontal cortical function during higher-order emotional processing with direct implications for our understanding and treatment of anxiety and trauma-related disorders.

PANEL • SATURDAY • 4:30 PM – 6:30 PM • PRIMROSE B

Feel Good Fuel: Mitochondrial Function in Reward Circuits
Chair: Cali Calarco

Presenters: Fiona Hollis, Cali Calarco, Emily Witt, Sergio Dominguez-Lopez

Altered motivational states associated with depression or substance use disorders are accompanied by molecular and cellular changes in brain regions important for reward processing. The prefrontal cortex (PFC), nucleus accumbens (NAc), and ventral tegmental area (VTA) have been extensively examined with respect to gene expression, electrophysiological activity, and neuronal morphology in response to stress or drugs. However, metabolic activity and cellular metabolic support of reward-related changes have been comparatively underexplored. In this panel we look at mitochondria to see how the powerhouse of the cell fuels reward-related brain changes. Dr. Fiona Hollis (University of South Carolina) will prime us to think about mitochondria mediating behavior and share findings that females exposed to gestational stress exhibit reduced PFC mitochondrial respiration correlating with depressive-like behavior and cytokines in a rat model of postpartum depression. Dr. Cali Calarco (University of Maryland, Baltimore) will share the response of NAc mitochondria to cocaine and nicotine in mouse models, showing changes in mitochondria-related gene expression, mitochondrial respiration, and cell-type selective medium spiny neuron dendritic morphology. Dr. Emily Witt (Dalhousie University) will show cocaine self-administration changes mitochondrial morphology in NAc astrocytes, increasing size, which normalizes after extinction training. Finally, Dr. Sergio Dominguez-Lopez (University of Maryland, Baltimore) will show long-term methamphetamine self-administration induces changes in the redox environment and mitochondria respiration along the mesolimbic pathway that coincide with resetting of dopamine firing homeostasis in the VTA. These findings link dopamine neurotransmission and mitochondrial bioenergetics. Together we will outline mitochondrial responses in reward-related brain regions to altered motivational states, approaching an understanding of cellular fuel for reward.

PANEL • SATURDAY • 4:30 PM – 6:30 PM • SUPERIOR

Novel Insights into the Brain Circuit Adaptations Underlying Substance Use Disorders

Chair: Stephan Lammel

Presenters: Adelaide Minerva, Abigail Polter, Stephan Lammel, Sung Han

Substance use disorder (SUD) is a major public concern worldwide. To develop more effective treatment strategies, it is important to gain a better understanding of the neurobiological changes that underlie addiction. Current hypotheses of addiction have often focused on how drugs of abuse create reward-processing pathogenesis, whereby drug-induced activation of VTA dopamine neurons leads to a cascade of adaptations which eventually give rise to aberrant forms of learning that contribute to the development of SUD. However, negative stimuli and events also engage the VTA and can induce both adaptive and maladaptive plasticity. Indeed, one of the hallmark features of SUD is drug seeking behavior despite the potential for adverse or negative consequences. Therefore, examining how stress and other negative stimuli induce cellular and synaptic adaptations is critical for our understanding of the neurobiological basis of addiction. In this panel, we will present novel perspectives on how positive or negative affective states lead to behavioral changes through modulation of plasticity in the mammalian brain. Adelaide Minerva (Princeton) will share results of unique transcriptional signatures of resilience and susceptibility to stress in the VTA using single-nucleus RNA-seq. Abigail Polter (George Washington U) will demonstrate sex-specific stress induced plasticity of VTA synapses and discuss how VTA microcircuitry adapts during the progression from acute to chronic stress. Stephan Lammel (UC Berkeley) will provide a mechanistic circuit-level understanding of the neurobiological underpinnings underlying nicotine's dose-dependent effects on reward and aversion and the implications for nicotine addiction. Sung Han (Salk) will discuss evidence that discrete opioidergic circuits mediate different aspects of opioid-induced adaptive behaviors (i.e., opioid preference versus seeking) by responding oppositely to morphine.

PANEL • SATURDAY • 4:30 PM - 6:30 PM • WASATCH A

Neuroscience Education: The Power of Training Faculty to Incorporate Research Into Their Teaching

Chair: Sonsoles de Lacalle

Presenters: Paul Ulrich, Christy Visaggi, Sonsoles de Lacalle, Thomas Clobes

Creating faculty learning communities is a powerful approach to multi-disciplinary engagement; drawing upon the diverse strengths of faculty from varied research foci fosters creativity, widens the breadth of inquiry and offers solutions by 'thinking outside the (disciplinary)box'. This is particularly key in neuroscience, a multidisciplinary field that benefits from the application of Course-based Undergraduate Research Experiences (CUREs) where a whole class tackles a research question. A hands-on activity is one of the best predictors of student perseverance in STEM, and highly effective in developing science identity and sense of fit in minoritized students. This panel aims to address the notion that designing/implementing CUREs is costly and time consuming, by presenting the perspective of both trainers and trainees engaged in a model workshop that operationalizes a multidisciplinary learning community approach. Sharing insights on design and delivery, this panel will engage attendees to join in discussion utilizing sample materials, in an interactive presentation.

In her introduction, S. de Lacalle (CSUCI—Health Science) will provide a background for this work, and lead the ensuing discussion. Presenting the structure and modular organization of a highly adaptable workshop supporting development of CUREs, P. Ulrich (GSU—Biology) will share a suite of deliverables that allows to sustainably design major components of CUREs. Next C. Visaggi (GSU—Geosciences) will explain how to effectively engage faculty online and across disciplines, using accessible tools. S. de Lacalle will then describe a faculty learning community format that encourages multi-disciplinary engagement, and how learning from those from different research foci can expand one's instructional toolbox. Finally, T. Clobes (CSUCI—Health Science) will present the process of implementing a CURE on the uses of medical cannabis, resulting in a publication and several research proposals.

PANEL • SATURDAY • 4:30 PM – 6:30 PM • WASATCH B

mTOR Signaling in Autism Spectrum Disorders

Chair: Stephen Smith

Presenters: Stephen Smith, Smita Yadav, Damon Page, Helen Bateup

Multiple lines of evidence implicate mTOR dysregulation in Autism Spectrum Disorder (ASD), and suggest mTOR signaling networks may be one “convergent mechanism” linking multiple genetic forms of ASD. Given the availability of mTOR-modifying drugs, a better mechanistic understanding of mTOR’s role in neural development and homeostasis offers a rare clinical opportunity for treatment of ASDs. Stephen Smith will give an overview of the mTOR pathway, and introduce a protein interaction network approach to monitoring mTOR signaling. Using immortalized cells and neurons undergoing homeostatic plasticity, Dr. Smith will present a novel non-linear model of mTOR signal transduction, in control and ASD-mutation-carrying cells. Smita Yadav will discuss TAOK1, a serine-threonine kinase strongly associated with both ASD and neurodevelopmental delay (NDD). Recent work from Dr. Yadav’s lab demonstrates that TAOK1 interacts with both mTOR and Hippo pathways as it directly associates with phosphoinositides to remodel the plasma membrane, dysfunction of which contributes to the etiology of neurodevelopmental disorders. Damon Page will discuss ongoing work identifying convergent mechanisms across forms of ASD and intellectual disability that feature abnormal trajectories of brain growth, i.e. macrocephaly and microcephaly. Dr. Page will discuss the identification and implications of dysregulated growth factor and mTOR signaling in the developing cerebral cortex in models of PTEN and DYRK1A haploinsufficiency. Helen Bateup will discuss mouse models of the ASD Tuberous Sclerosis Complex (TSC) and show how alterations in mTOR signaling affect the biochemistry, morphology and physiology of different types of neurons. Dr. Bateup will present findings showing that genetic manipulation of the mTORC1 protein Raptor can be an effective therapeutic strategy for multiple neurodevelopmental phenotypes associated with TSC.

SATURDAY EVENING PANELS

SHORT COURSE • SATURDAY • 7:00 PM – 8:30 PM • BALLROOM I

Using Microcontrollers for Neuroscience Research

Chair: Lex Kravitz
Presenters: Lex Kravitz, Jibran Khokhar, Jude Frie

Do you want to build custom equipment for your experiments but don't know where to start?Do you want to add functionality to an existing piece of hardware, or implement a new behavioral task that is not sold commercially? In this short course you can learn how to get started coding micro-controllers and developing novel hardware, using the free and open-source Arduino development environment. The course will be led by Lex Kravitz, Jude Frie, and Jibran Khokhar. We will provide a practical introduction to the Arduino programming language and provide hardware for participants to use to gain hands-on experience. The course will start from the basics – no coding required! – with the goal of onboarding new users and getting them started controlling hardware devices. As a group we will learn about how microcontrollers work, how to configure them, and build a programmable function generator that we can use to control an optogenetic stimulation system. While the in-person course content will be focused on getting started, we will also provide more advanced "hybrid" virtual content to all participants so they can continue learning on their own.

PANEL • SATURDAY • 7:00 PM – 8:30 PM • MAGPIE A

Lost in Vagus: Deregulation in Vagal Signaling in Health and Disease

Chair: Jasenka Zubcevic
Presenters: Guillaume de Lartigue, Teresa Pitts, Jasenka Zubcevic

As the great wandering nerve, the vagus in involved in a cross-disciplinary set of functions. From the airway to the colon, scientists are targetting the vagus for restoration of function. Across our speakers we will highlight different efforts with the vagus as the common thread. First, Guillaume de Lartigue (Assoc Professor, Monell Institute) will show us how the GI vagus modulates feeding behaviors and how this may be deregulated in obesity. Teresa Pitts (Assoc Professor, University of

Louisville) will show the impact spinal cord injury altering vagal afferent and efferent signaling in the larynx, and how targeting these pathways can restore swallow function- a first of its kind. Lastly, Jasenka Zubcevic (Assoc Professor, University of Toledo) will present her foundational work on the select vagal afferent signaling from the gut in regulation of blood pressure and how this may be modified by gut bacterial dysbiosis.

PANEL • SATURDAY • 7:00 PM – 8:30 PM • MAGPIE B

Prodromal Synucleinopathy Neuroimaging Update

Chair: Daniel Huddleston

Presenters: Kejal Kantarci, Daniel Huddleston, Xiaoping Hu

Neurodegeneration in the synucleinopathies, i.e., dementia with Lewy bodies (DLB), Parkinson's disease (PD), and multiple system atrophy (MSA), begins well before clinical diagnosis. Patients with idiopathic REM sleep behavior disorder (iRBD) are at high risk of future phenoconversion to overt DLB, PD, or MSA. An important translational research goal is the development of neuroimaging tools to detect and monitor prodromal neurodegeneration in iRBD. The presenters lead the Neuroimaging Core for the new North American Prodromal Synucleinopathy 2 (NAPS2) study funded by the NIH-NIA.

Talk #1: Kejal Kantarci, MD - Differences in regional metabolism are observed using fluorodeoxyglucose PET in structures implicated in early synucleinopathy in a study of individuals with iRBD who progress clinically vs. iRBD who remain clinically stable. Amyloid PET reveals the gradual emergence of amyloid pathology in vivo across the natural history of synucleinopathy from iRBD to DLB.

Talk #2: Dan Huddleston, MD - The hippocampal subfields are established sites of neuropathology in the Lewy body dementias, but this has not been observed previously in vivo. Progressive changes in hippocampal subfield microstructure, observed using a high-resolution diffusion MRI approach, are observed in overt Lewy body dementias as compared to iRBD.

Talk #3: Xiaoping Hu, PhD - Many brain regions implicated in synucleinopathy biology are small brainstem and limbic structures, such as the hippocampal subfields, substantia nigra, and locus coeruleus. This poses a technical challenge for MRI research. Issues to be discussed include 1) achieving adequate spatial resolution, 2) motion issues, and 3) detecting effects in nigral subregions.

SHORT COURSE • SATURDAY • 7:00 PM – 8:30 PM • PRIMROSE A

Pipette-Free Drug Repurposing for CNS Disorders

Chair: Robert McCullumsmith

Presenters: Robert McCullumsmith, Sinead O'Donovan, Rammohan Shukla

Repurposing (or first purposing) library-indexed compounds and/or FDA approved drugs is gaining momentum, due to availability of large publicly available databases and efficient bioinformatics tools for drug identification. An overview of the general strategies for drug repurposing will be provided, with specific examples from laboratories that have successfully adopted in silico repurposing strategies despite beginning the process with no bioinformatics footprint. Novel in silico strategies for drug repurposing, accessible for laboratory scientists, will be presented, including transcriptional profiling and structure-function based approaches. The primary goal of this course is to provide the learners a better understanding of how bioinformatics tools may be deployed to facilitate laboratory-based research, as well as testing hypotheses in silico before wet-lab resources are committed. Dr. Robert McCullumsmith, a laboratory scientist who has successfully deployed in silico bioinformatics approaches to identify drugs for repurposing, will provide an overview of repurposing strategies and examples of success stories. Dr. Sinead O'Donovan will discuss transcriptional profiling and database mining for repurposing. Dr. Rammohan Shukla will discuss structural profiling approaches for repurposing. Learning objectives for the session include 1) gaining perspectives for how bioinformatics can be used to identify new leads for pharmacological treatments, 2) highlighting the tools and databases available to facilitate in silico drug repurposing, and 3) providing a foundation for understanding how transcriptional and structural profiling may be deployed for drug repurposing.

PANEL • SATURDAY • 7:00 PM – 8:30 PM • PRIMROSE B

Interactions Between Substance Use and Aging in Animal Models

Chairs: Barry Setlow, Cassandra Gipson

Presenters: Cassandra Gipson, Mathieu Wimmer, Shameena Bake, Barry Setlow

As the number of people living to advanced ages has grown, the impact of substance use on healthy brain function in older adults is of increasing concern. Understanding of how substance use interacts with the aging brain is hampered, however, by a paucity of preclinical research that has addressed these interactions. The participants in this panel will present recent data from studies in rodent models that show multiple unique ways in which substance use and various aspects of the aging process can interact to influence behavior and neurobiology. Cassandra Gipson will discuss contributions of ovarian hormone loss and estrogen replacement to nicotine place preference in estropausal and post-estropausal female rats. This issue is important because the variability and eventual precipitous loss of ovarian hormones during the menopausal transition in women may interact with SUD progression and thus hinder treatment outcomes for nicotine dependence and/or pathological aging. Mathieu Wimmer will discuss data from a drug self-administration paradigm in aged rats, as well as apparent parallels between age- and drug-induced deficits in hippocampus-dependent memory in male and female rats, which could offer a unique approach to better understanding neural mechanisms engaged by chronic drug use in aged subjects. Shameena Bake will discuss data from rats showing that prenatal alcohol exposure exacerbates both acute and long-term consequences of stroke on sensory-motor and cognitive function in middle age. Barry Setlow will discuss data in rats showing that chronic voluntary oral THC consumption enhances cognitive performance in aged rats of both sexes, but has limited or no effects in young adult rats. Collectively, these data highlight numerous ways in which drugs of abuse can have distinct effects during the aging process, and they serve as a foundation for future research on this important topic.

PANEL • SATURDAY • 7:00 PM – 8:30 PM • SUPERIOR

Mechanisms Linking Chronic Pain and Substance Use Disorders: A Focus on Pain Catastrophizing

Chair: Patrick Finan

Presenters: Robert Edwards, Lara Ray, Vitaly Napadow

Pain is highly prevalent among patients with substance use disorders, and chronic pain in particular is a common comorbidity. Evidence suggests the relationship is bidirectional, with pain increasing risk for substance use disorders, and vice versa. As such, there is a substantial interest in unpacking the basic mechanisms and shared factors that promote this association. In this panel, we focus on the transdiagnostic cognitive-emotional process called catastrophizing. Pain catastrophizing is a negatively valenced pain coping strategy characterized by rumination, magnification, and/or helplessness about the experience of pain. It is associated with deficits in reward system function, and improvements in neurophysiological reactivity to rewarding stimuli are associated with improvements in pain catastrophizing among patients with chronic pain. The speakers in this panel will highlight converging lines of evidence supporting the role of pain catastrophizing as a mechanism contributing to the shared risk of pain and substance use disorders. Dr. Robert Edwards will provide an overview of pain catastrophizing and present his extensive research into the association of pain catastrophizing with opioid use behaviors. Dr. Lara Ray will then present translational work from her lab that has demonstrated the reward system-mediated role of pain catastrophizing in alcohol use disorder. Dr. Vitaly Napadow will then present his work on neural correlates of pain catastrophizing in patients with fibromyalgia, a chronic pain disorder characterized by deficits in positive emotions and reward system function. Following the panel presentations, Dr. Patrick Finan will moderate a discussion about the common threads connecting pain catastrophizing to risk for comorbid chronic pain and substance use disorders. The discussion will emphasize how pre-clinical and clinical research can inform efforts to optimize treatment and prevention.

PANEL • SATURDAY • 7:00 PM – 8:30 PM • WASATCH A

Reefer Madness: Revisiting the Intersectionality Between Cannabis, the Endocannabinoid System, and Psychosis

Chair: Mary Torregrossa

Presenters: Shinnyi Chou, Sierra Stringfield, Bryan Jenkins

Cannabis is one of the most widely used psychoactive substance among adolescents, with a steady increase in use over the past decade. Cannabis use is associated with various psychiatric comorbidities and represents one of the strongest environmental risk factors for psychotic disorders. Cannabis exposure tends to precede onset of psychotic symptoms in those with primary psychotic disorder, and many patients diagnosed with cannabis-induced psychosis also go onto develop primary psychotic disorders. Patients with psychotic disorders also use cannabis at much higher rates, and are diagnosed frequently with a cannabis use disorder, which is associated with a worsening of the course of the psychotic disorder. As such, increasing our understanding of the relationship between cannabis use, the endocannabinoid system, and psychosis is of critical importance given the rapid increase in cannabis legalization across the globe. The aim of the current symposia is to present recent studies in the field of cannabis use, endocannabinoid system, and their roles in psychosis from cellular, animal model, to human studies, highlighting the translational value of each unit of analysis in guiding potential therapeutic interventions. First, Shinnyi Chou will present findings using non-human primate and human post-mortem samples regarding the cell-type specific distributions of the cannabis receptor type 1 within different brain regions. Next, Sierra Stringfield will share novel data using rodent THC self administration in adolescents to describe long-term, sex-specific effects on prefrontal cortical neural activity during working memory as measured using in vivo calcium imaging. Finally, Bryan Jenkins from Dr. Jibran Khokhar's lab will describe novel studies from rodents used to neurodevelopmentally model schizophrenia and experimentally naïve animals to detect changes in neural circuit oscillatory activity and schizophrenia-like behavior after exposure to vaporized cannabis flower.

PANEL • SATURDAY • 7:00 PM – 8:30 PM • WASATCH B

Post-Traumatic Epilepsy Models and Biomarkers

Chair: Dominique Duncan

Presenters: Denes Agoston, John Wolf, Dominique Duncan

Post-traumatic epilepsy (PTE), defined by delayed onset of recurrent seizures is one of the major complications following traumatic brain injury (TBI). The epileptogenic process leading to PTE is currently poorly understood but is likely multifactorial and crosses multiple modalities. Without a full understanding of the underlying pathobiological process, there will be no cures for PTE. There is a need for the development of effective translational animal PTE models to better understand the underlying pathophysiology and provide treatment, as well as diagnostic and prognostic biomarkers for PTE.

Denes Agoston (USUHS) will discuss the complex damage after TBI by evaluating blood- and cerebrospinal fluid (CSF)-based protein biomarkers of epileptogenesis. Different types of injury (e.g. penetrating vs closed-head) result in different biological responses (e.g. neuroinflammation, glial damage) which must be identified using unique biomarkers. Determining the temporal profile of protein biomarkers in the blood and CSF can help to identify pathobiologies underlying the development of PTE, high-risk individuals, and disease modifying therapies.

John Wolf (UPenn) will describe his work on modeling PTE in a gyrencephalic large animal, the pig. His work aims to understand the contributions of various injury components such as inertial and focal injury to the brain in the development of PTE. Following TBI, high density electrodes are implanted in the pig brain. The animals are monitored for several months post-injury and video-EEG and blood biomarkers are studied as potential prognostic measures for the development of PTE.

Dominique Duncan (USC) will present harmonization, quality control, and analytic tools developed for multimodal rodent and human TBI data. A centralized data archive with a variety of analytic tools has been developed to identify and validate biomarkers of epileptogenesis in imaging and electrophysiology as well as in molecular, serological, and tissue data.

Sunday, January 22, 2023

SUNDAY MORNING PANELS

PANEL • SUNDAY • 7:30 AM – 9:30 AM • BALLROOM I

Incubation of Drug Craving: From Genes to Circuits to Humans
Chair: Yavin Shaham
Presenters: Marina Wolf, Mathieu Wimmer, Ida Fredriksson, Muhammad Parvaz

In 2001, Grimm et al. reported that cocaine seeking progressively increases after cessation of drug self-administration in rats, a phenomenon termed 'incubation of drug craving.' Subsequently, this incubation phenomenon has been shown with other addictive drugs, is considered a model of relapse vulnerability, and has inspired mechanistic preclinical studies and clinical translation. Our panel will describe new studies on cellular, transcriptomic, and circuit mechanisms of incubation of drug craving, as well as objective assessment of incubation and underlying mechanisms in humans.
Wolf (OHSU) will present unpublished data showing that homeostatic synaptic plasticity mediated by retinoic acid signaling is responsible for the strengthening of nucleus accumbens (NAc) synapses that ultimately mediates incubation of cocaine craving.
Wimmer (Temple) will present findings on cell-type specific transcriptomic changes in NAc Drd1- and Drd2-expressing cells during early and late withdrawal and their association with incubation of heroin craving.
Fredriksson (NIDA) will introduce a model of potentiated incubation of oxycodone craving after electric barrier-induced abstinence and will describe results on the role of ventral subiculum (vSub) neuronal ensembles and vSub circuits (assessed by anatomical and fMRI methods) in this new form of incubation.
Parvaz (Mount-Sinai) will describe the use of psychophysiological techniques to quantify incubation of cocaine and methamphetamine cue-reactivity in humans. He will also show data on the effect of cognitive reappraisal to mitigate cue reactivity and discuss ongoing work on neurobiological mechanisms of human incubation of drug craving.
We will conclude by discussing with the audience the incubation phenomenon and its relevance to human relapse and addiction treatment.

PANEL • SUNDAY . 7:30 AM - 9:30 AM • MAGPIE A

Memory Engrams are Altered During Stress, Aging, and Anxiety

Chair: Holly Hunsberger

Presenters: Kevin Sattler, Kirstie Cummings, Holly Hunsberger, Stephanie Grella

How memories are acquired, stored, and retrieved has fascinated scientists since the time of Plato and Aristotle. In the 20th century, Richard Semon coined the term, “engram,” to describe a neural substrate for memory. Engrams are activated by learning, endure cellular changes, and are reactivated by the original stimulus. Although we have made great strides in understanding memory formation, we have yet to determine how stress, maladaptive states, aging, and neurodegeneration impact memories over time. Here, we aim to address how memory engrams change in response to aging, stress, anxiolytic treatments, and how they are incorporated into our neural network of past experiences. The panel gathers expertise from new investigators in the field of memory research spanning molecular, cellular, and circuit level analysis. Kevin Sattler will first explain the role of the ventral hippocampus in trauma encoding, but also aim to delineate how ventral hippocampal projections modulate social behaviors (i.e. increases in aggression and fear) following a traumatic experience using chemogenetic manipulations, retrograde tracing, and activity-dependent tagging. Dr. Kirstie Cummings will then demonstrate how a novel engram population in the ventromedial prefrontal cortex regulates cued fear memory by using activity-dependent tagging, optogenetics-assisted whole-cell electrophysiology, and in vivo optogenetics and fiber photometry. Dr. Holly Hunsberger will discuss the sex-specific short and long-term effects of benzodiazepines on memory encoding and retrieval using activity dependent tagging models, behavior, and miniscopes. Lastly, Dr. Stephanie Grella will explain how we can potentially reset our memories and re-establish cognitive and behavioral flexibility by targeting the dentate gyrus using activity-dependent tagging models and optogenetics.

PANEL • SUNDAY . 7:30 AM - 9:30 AM • MAGPIE B

Brain Dynamics and Nonlinearity During Functional Reorganization

Chair: Stefan Posse

Presenters: Todd Constable, Xiaoping Hu, Essa Yacoub, Stefan Posse

T. Constable - Connectome studies generally assume spatially stationary node definitions that can be improved using structure constraints from DTI or myelography. This assumption is now challenged by evidence for flexible brain organization at all scales. We discuss flexible functional organization within a fixed infrastructure, implications on research of the connectome and solutions that take into consideration functional flexibility.

X. Hu - We characterized phase space dynamics of resting-state fMRI with sum of edge lengths (SE) in the reconstructed phase portrait. The method detected a significant increase in SEs in networks in autistic patients and enabled classification of autistic and schizophrenia patients. Phase space embedding is a powerful approach for characterizing nonlinear BOLD signal dynamics and identifying changes in nonlinear network dynamics in neuropsychiatric disorders.

E. Yacoub - Unprecedented sub-second temporal resolution of fMRI has improved statistical power and characterization of the hemodynamic response function (HRF). This high temporal sensitivity has translated into improved spatial characterization of neuronal responses to separate different vascular compartments based on temporal differences in their HRF and to differentiate deeper laminae having faster or superficial layers having slower responses.

S. Posse – There is growing evidence for signal fluctuations at frequencies beyond traditional resting-state fMRI made possible by high-speed fMRI and frequency segmented regression of confounding signals. High frequency fluctuations have been shown to increase during sleep and they are preserved after functional reorganization around brain tumors, opening a new window into temporal-spatial network dynamics.

PANEL • SUNDAY • 7:30 AM – 9:30 AM • PRIMROSE A

The Insula: An Integral Hub for Motivation and Affect

Chair: Samuel Centanni

Presenters: Amy Lasek, Samuel Centanni, Ashmita Mukherjee, Dennis Sparta

Dysfunctional emotional regulation is highly comorbid with many neuropsychiatric disorders including affective and substance use disorders. The insula is an expansive brain area spanning the anterior-posterior gradient in the brain, and specific insular subregions seem to uniquely contribute to emotional and motivational behavioral output through intricate circuitry with cortical and subcortical brain regions. However, the precise circuitry and molecular mechanisms governing the insula's involvement in these behaviors has not been fully elucidated. This panel will present exciting new data using an array of techniques ranging from synaptic activity to rodent behavior to explore different insula-centric circuitry in stress and alcohol use disorder- with an emphasis on a role in alcohol drinking behavior. First, Amy Lasek (VCU) will present the results of RNA-Sequencing of the mouse insula, comparing differential gene expression between short-term and long-term ethanol drinking. Next, Sam Centanni (Wake Forest), will discuss recent work examining a unique motor cortex-mid-insula-BNST circuit that is involved in monitoring active escape behavior during an inescapable stressor and subsequent negative affect behavior. Ashmita Mukherjee (U. Buffalo) will then present data demonstrating that insular dopaminergic innervation contributes to the development of escalated alcohol intake as well as impacts learning about the deleterious consequences of alcohol consumption. Lastly, Dennis Sparta (UIC) will present work describing a novel insula to ventral BNST circuit that modulates reward-related behavior and is altered by binge alcohol consumption. Together, this session will detail novel data focused on an exciting brain region emerging as an integral regulator of behavioral output. Interventional strategies aimed at mitigating dysfunctional insula circuitry can have broad implications for curbing affective and motivational states driving stress and alcohol use disorders.

PANEL • SUNDAY • 7:30 AM – 9:30 AM • PRIMROSE B

Synaptic Adhesion Molecules and Disease: From Molecules to Circuits

Chairs: Katherine Roche, Marc Fuccillo
Presenters: Katherine Roche, Tabrez Siddiqui, Adema Ribic, Marc Fuccillo

Accumulating evidence from human genetics studies reveals that mutations in synaptic genes play a central role in the etiology of neurodevelopmental and psychiatric disorders. The highest confidence genes include those encoding synaptic cell adhesion molecules, proteins that mediate the development and maintenance of neural connectivity. Our session will explore the multi-faceted functions of synaptic adhesion molecules and how mutations in these genes lead to disease relevant cellular and circuit alterations. Katherine Roche will discuss her lab's research on autism-associated mutations in neuroligins and the trafficking defects resulting from these rare variants. In addition, she will examine downstream signaling pathways contributing to synapse function, including the RhoGEFS, Kalirin and Trio. Tabrez Siddiqui will discuss how synapse organizing proteins coordinate the broad spectrum of synapse development, including formation and maintenance of synapses, as well as experience-dependent changes in synaptic strength. He will demonstrate cell-type and developmental-stage-specific functions of synapse organizers in fine-tuning neuronal circuit connectivity and plasticity. Adema Ribic will discuss work on how synaptic adhesion molecules restrict plasticity and learning in a synapse-selective manner. She will show work on SynCAM1/CADM1 knockout (KO) mice, that show increased cortical plasticity and accelerated learning in perceptual tasks despite deficits in synapse formation and abnormal circuit physiology. Finally, Marc Fuccillo will examine the contributions of Neurexin1a, a presynaptically-localized adhesion molecule, to the function of cortical and striatal circuits supporting reinforcement learning, a key behavioral endophenotype spanning neuropsychiatric conditions. The Fuccillo lab has found that Neurexin1a disruption impacts multiple nodes within cortico-basal ganglia circuits critical for this essential behavioral function.

PANEL • SUNDAY • 7:30 AM – 9:30 AM • SUPERIOR

I 'Snow' How you Feel: Using Rodent Models to Understand the Neurobiology of Empathy

Chairs: Monique Smith, James Burkett
Presenters: James Burkett, Weizhe Hong, Hee-Sup Shin, Monique Smith

Empathy is a core social ability that is critical for social functioning, yet little is known about the biological mechanisms that participate in sensing and responding to the emotions of others. Historically, empathy was considered an affective-cognitive process experienced solely by humans. However, it is now appreciated that many species, including rodents, display empathy-related behaviors. A wave of recent research has demonstrated that various types of rodent empathy depend upon neural structures and neurotransmitters homologous to those involved in human empathy. This panel includes researchers at the forefront of this exciting research area, and each presenter will discuss their work demonstrating evidence for convergent neural mechanisms of empathy across unique rodent models.

Dr. Burkett will present research on the neuromolecular basis of consoling behavior in the prairie vole, in the context of a theoretical framework for understanding empathy-related behavior in animal models. He will also show the application of this research to translational models for autism. Dr. Hong will present work showing that mice display prosocial comforting behavior toward partners. He will also discuss the role of the amygdala and hypothalamus in recognizing another's emotional state and promoting comforting behavior. Dr. Shin's work uses the observational fear paradigm in rodents, a robust model for emotional contagion. Dr. Shin will present data demonstrating that the anterior cingulate (ACC) and amygdala are essential for observational fear, and discuss recent results that reveal how multiple brain regions interact to drive affective empathy. Dr. Smith will present her work which demonstrates that mice rapidly acquire the sensory and emotional state of their social partners. She will also discuss how this social transfer of pain requires the ACC and that the ACC utilizes distinct pathways to generate appropriate and matched behavioral states in social partners.

PANEL • SUNDAY • 7:30 AM – 9:30 AM • WASATCH A

Mapping Theoretical and Basic Research Findings of Cognitive Aging to Older Adult's Everyday Life Concerns

Chair: Rachael Seidler
Presenters: Abbi Hernandez, Joaquin Anguera, Rachael Seidler, Natalie Ebner

We will present new findings on the determinants of cognitive aging, spanning behavioral neuroscience approaches in rodents up to real-world concerns in aging humans such as being vulnerable to exploitation and managing mobility declines. Dr. Seidler will introduce the session, highlighting links to popular media and science, arguing for ecologically valid research paradigms for more impactful translation. Dr. Hernandez will show new findings comparing time restricted feeding effects with and without ketogenic diet. She will show that time restricted feeding mediated most of the gut microbiotic changes observed, but that there were also some changes specific to ketogenic diet. Time restricted feeding is easier to implement and maintain than a ketogenic diet, suggesting an optimal route for improved cognition in older adults. Dr. Anguera will describe distinct digital and mHealth approaches for improving cognitive control in older adults, describing how these can be leveraged for a more individually tailored experience. Dr. Seidler will present on the effects of walking and imagined walking on varying uneven terrain levels (a high fall risk condition in older adults); she will address whether load manipulations under these naturalistic conditions elicit similar patterns of brain activity to working memory load manipulations. Dr. Ebner will present recent findings on the ability of older adults to detect deception (e.g., phishing, fake news), a topic that is critically important in our current era of subjective, sensationalized news and with increasing exploitation rates among older adults. She will share that vulnerability to deception occurs primarily among the oldest old and is linked to analytical reasoning abilities; she will also discuss data toward identifying a neurosignature of vulnerability to deception. Dr. Seidler will close with discussion of mapping theoretical and basic research findings of cognitive aging to older adults' everyday life concerns.

PANEL • SUNDAY • 7:30 AM – 9:30 AM • WASATCH B

Novel Tools to Map Adaptive and Maladaptive Effects of Reactive Astrogliosis in CNS Diseases

Chair: Milos Pekny
Presenters: Milos Pekny, Jan Mulder, Rudolf Merkel

It is now well appreciated that neuropathologies such as neurotrauma, intracerebral hemorrhage, ischemic stroke or neurodegenerative diseases (e.g., Alzheimer's disease or ALS) trigger reactive astrogliosis. The molecular signatures and functional consequences of astrocyte reactivity are at least partially disease-specific, may become adaptive or maladaptive, and in some disease contexts present attractive therapeutic targets. Understanding the context-specific molecular phenotype of astrocytes will provide novel strategies for diagnostics and intervention in neurological diseases. This panel will focus on the novel state-of-the-art technologies which allow to identify specific rheological, molecular and functional consequences of astrocyte reactivity and reactive astrogliosis in several CNS diseases. Milos Pekny will introduce the concept and demonstrate how high-resolution in vivo fMRI has most recently revealed an important role of reactive astrocytes in post-stroke neuronal connectivity. He will also discuss novel insights into the mechanisms through which modulation of astrocyte reactivity improves functional outcome after intracerebral hemorrhage. Jan Mulder will demonstrate the unprecedented power of spatial transcriptomics in molecular mapping of astrocyte responses in CNS pathologies, and show the value of the open access Human Protein Atlas with 55 000 polyclonal antibodies for exploitation of novel astrocyte signature proteins. Rudolf Merkel will present current state-of-the-art methods to assess cell mechanoresponses and rheology parameters, including atomic force microscopy, and demonstrate how they can advance the understanding of the responses of reactive astrocytes to cellular stress.

SUNDAY AFTERNOON PANELS

PANEL • SUNDAY • 4:30 PM – 6:30 PM • BALLROOM I

Ketamine Can Get You High But is it a Better Lift?

Chair: Elyssa Margolis
Presenters: Lakshmi Devi, Tommaso Di Ianni, Marjorie Levinstein, Matthew O'Meara

Ketamine, an NMDA receptor (NMDAR) antagonist at the PCP site, was approved in 1970 for clinical use as an anesthetic. Currently, subanesthetic doses of ketamine, a racemic mixture of (R)- and (S)-enantiomers, are used to rapidly improve pain and depressive symptoms. Despite fast clearance, these effects last for days after a single dose. What are the pharmacological mechanisms of action that generate these beneficial effects, and can they be isolated from ketamine's adverse effects? Margolis (chair) will introduce the session, providing background on ketamine's chemistry and established pharmacology. Devi will discuss ongoing studies of non-NMDAR mediated molecular actions of ketamine. She will provide evidence that ketamine acts as a positive allosteric modulator of endogenous opioid peptide-engaged mu opioid receptors (MORs). Di Ianni will next discuss unpublished findings that blocking opioid receptors modulates neurophysiologic changes evoked by ketamine, but not by a selective NMDAR antagonist, using functional ultrasound imaging in rats. This opioid-mediated response was only evident in males, and in brain regions implicated in depression and reward processing. Levinstein will then describe the pharmacology of ketamine's enantiomers and the bioactive metabolite (2R,6R)-hydroxynorketamine, showing how these relate to abuse liability and depression. For instance, (S)-ketamine is the main contributor to abuse liability, an action involving MORs. Finally, O'Meara will describe chemoinformatic strategies to predict and dissect polypharmacology. He will describe a polypharmacology case study of an NMDAR antagonist with similar antidepressant effects to ketamine. It shows synergistic signaling between GPCRs and NMDARs at KCNQ potassium channels that also contribute to ketamine's actions. Together we highlight how non-NMDAR sites produce both therapeutic and adverse ketamine effects, thus providing new understanding and mechanistic targets for drug development.

PANEL • SUNDAY • 4:30 PM - 6:30 PM • MAGPIE A

Function and Mechanism of Signaling Mediated by the Ionotropic Glutamate Receptors

Chair: Terunaga Nakagawa

Presenters: Terunaga Nakagawa, Maria Kurnikova, Jakob von Engelhardt, Lonnie Wollmuth

Ionotropic glutamate receptors (iGluRs) play pivotal roles in synaptic and extra-synaptic signaling by functioning as ligand-gated ion channels activated by the neurotransmitter glutamate. Physiological processes that are regulated by the iGluRs include, although not limited to, synaptic plasticity, synapse maturation, and circuit development. Dysfunctions of iGluR are related to a variety of neurological and psychiatric disorders, and thus understanding the biology and mechanism of their signaling are critical for identifying new therapeutic targets that may alleviate various disease conditions. Each panelist will discuss recent findings related to the signaling of AMPA and NMDA subtypes of iGluRs. Nakagawa will present new high resolution cryo-EM structures that provide insights into the mechanism of ion permeation in AMPA receptors. Kurnikova will talk about the mechanism underlying subconductance states in AMPA receptors obtained by MD simulations. Von Engelhardt will present how modulation of AMPA receptors by auxiliary subunits regulate the synaptic plasticity in visual thalamic circuits. Wollmuth will present about the pivotal roles of non-synaptic signaling mediated by NMDA receptors during the development of zebrafish. The panel will introduce iGluR signaling from different angles ranging from molecular structure, MD simulation, synaptic physiology, circuit function, to development.

PANEL • SUNDAY • 4:30 PM - 6:30 PM • MAGPIE B

NADIA: Cholinergic Regulation of Neuronal Plasticity and Disruptions by Adolescent Alcohol

Chair: Fulton Crews

Presenters: Ryan Vetreno, Lisa Savage, Kati Healey, Victoria Macht

Neurobiological consequences of adolescent alcohol exposure persist long into adulthood, despite abstinence. At the center of these lasting changes are alcohol-induced long-term disruptions to the central cholinergic system, which has repercussions on neuronal excitability, glial function, and cellular and behavioral plasticity. This panel aims to synthesize an evolving area of research on persistent adult changes following a model of an underage drinking, adolescent intermittent ethanol (AIE), on adult cognition as well as cortical, hippocampal and forebrain cholinergic pathology. Ryan P. Vetreno, University of North Carolina at Chapel Hill, will present findings on AIE-induced loss of adult forebrain cholinergic neurons related to REST epigenetic repression of the cholinergic transcriptome that can be reversed. Lisa Savage, Binghamton University, State University of New York, will present her findings on adolescent alcohol-induced loss of cortical acetylcholine release (microdialysis), nerve growth factor, and cognition including studies on reversal therapies. Kati Healey, Duke University, finds that AIE reduces activity and increases anxiety-like behavior in males, but increases risk-taking behavior in females, and both are prevented by dietary choline. In addition, data will be presented on AIE impairment of memory in both male and female rats. Victoria Macht, University of North Carolina at Chapel Hill, will present studies on how AIE-induced loss of hippocampal neurogenesis is linked to neuroimmune signaling induction, loss of hippocampal vesicular acetylcholine transporter expression, and male and female reversal learning and perseverative deficits. Findings highlight the role anti-inflammatory interventions in molecular and behavioral restoration. Collectively, these studies aim to synthesize the role of the cholinergic system both in the persistence of AIE brain pathology and also highlight its unique place in brain and behavioral interventions.

PANEL • SUNDAY • 4:30 PM – 6:30 PM • PRIMROSE A

Neural Mechanism Underlying Affective and Cognitive Interaction

Chair: Yi Zuo

Presenters: Paul Marvar, Shaorong Ma, Kuan Hong Wang, David Leopold

Complex mental processes often encompass both cognitive and affective components. While cognitive and affective processes engage distinct systems in the brain, their strong reciprocal anatomical connection and functional interaction are becoming increasingly appreciated. Such interaction is critical for adaptive decisions in a dynamic environment and is often impaired in neurological and psychiatric disorders. In this panel, Dr. Yi Zuo (University of California Santa Cruz) will give an overview of the intertwined neural circuits underlying affective and cognitive processes, and how affective states affect cognitive functions such as perception, learning, and decision-making, and vice versa. Dr. Paul Marvar (George Washington University) will talk about neural circuits of fear learning and novel methodology in rodent models for assessing real-time cardiovascular and autonomic measures of fear in changing threat-based environments. Dr. Shaorong Ma (University of California Santa Cruz) will present her new work on the frontoinsular interaction in a mouse behavior requires cognitive flexibility. Dr. Kuan Hong Wang (University of Rochester Medical Center) will discuss the role of frontal cortical dopamine projections in regulating cognitive and affective processes, and the cellular mechanisms underlying age-dependent plasticity in these projections. Dr. David Leopold (NIMH) will talk about primate brain architecture and neural neworks that enable high level visual interaction between individuals within a complex social environment. The panel will conclude with discussion and questions.

PANEL • SUNDAY • 4:30 PM – 6:30 PM • PRIMROSE B

Bottoms Up: The Gut-Brain Axis in Substance Use Disorders

Chairs: Santiago Cuesta, Kevin Braunscheidel

Presenters: Rebecca Hofford, Santiago Cuesta, Kevin Braunscheidel, Michelle Ren

Mechanisms related to the gut-brain axis have been proposed to modulate social, communicative, stress-related, and cognitive behaviors. Moreover, an altered gut microbiota composition and vagal nerve dysfunction have been associated with different neuropsychiatric diseases, including substance use disorders (SUDs). However, determining whether these peripheral changes cause, enhance or are the consequences of SUDs remains a challenge in the field.

This panel will discuss exciting new evidence revealing novel "bottom-up," body-to-brain signaling cascades that may impact addiction behaviors. First, Rebecca Hofford (Wake Forest School of Medicine) will present data showing how perturbations to the gut microbiome during adolescence – a crucial period for development of both the brain and the periphery – influence addiction-associated behaviors and drug reward brain circuitries. Second, Santiago Cuesta (Rutgers University) will show molecular evidence of how a change in adult gut microbiota composition, by altering the host's metabolic profile, can modulate the vulnerability to develop addiction in mice models. Third, Kevin Braunscheidel (Icahn School of Medicine at Mount Sinai) will describe how peripheral cholecystokinin signaling regulates nicotine intake via vagus nerve sensory afferents in mice. Finally, Michelle Ren will present findings from an animal model of intravenous fentanyl self-administration that supports a bidirectional role of gut bacteria in fentanyl use. More specifically, she will show the impact of fentanyl self-administration on gut bacteria as well as how gut bacteria depletion affects fentanyl self-administration.

Drug use and SUDs affect more than 27 million people in the United States; and yet, no successful evidence-based treatments have been developed. This panel will present current evidence of peripheral regulation of brain-reward circuitries, introducing the possibility of modulating the gut microbiome and the vagus nerve as strategies for the development of novel addiction therapies.

PANEL • SUNDAY • 4:30 PM – 6:30 PM • SUPERIOR

The Role of the Paraventricular Nucleus of the Thalamus in Motivated Behaviors

Chairs: Hao Li, Jacqueline McGinty
Presenters: Jacqueline McGinty, James Otis, Mario Penzo, Hao Li

The paraventricular nucleus of the thalamus (PVT) has been proposed as a critical hub connecting cortical and subcortical regions in regulating motivated behaviors. Further, the PVT contains a mix of neural populations with distinct anatomical and neurochemical features, which leads to heterogeneities in functions among different PVT pathways. However, we do not yet precisely know how different PVT neurons integrate inputs and orchestrate downstream pathways in mediating motivated behaviors. This question and more will be addressed by a diverse panel of investigators who represent multi-disciplinary perspectives. Dr. Jacqueline McGinty (MUSC) will discuss the circuitry and phenotypes of PVT neurons as revealed by intersectional viral vector tracing and gene expression in rodents. She will demonstrate the connectomics of PVT neurons that receive input from the prelimbic cortex and project to the nucleus accumbens (NAc) and the co-expression of mRNAs encoding kappa opioid receptors, mu opioid receptors, and D2 dopamine receptors in these neurons. Dr. James Otis (MUSC) will discuss paraventricular thalamic projections to parvalbumin interneurons (PV-IN) of the nucleus accumbens. He will focus on synaptic adaptions in the PVT to NAc PV-IN synapses that result from opioid or alcohol use, which in turn lead to adaptations in behavioral control. Dr. Mario Penzo (NIH) will discuss the role of PVT projections to the NAc in driving the learning of active avoidance behavior. Dr. Hao Li (Salk Institute) will discuss the role of PVT neurotensin (NT) neurons in regulating valence assignment in the basolateral amygdala (BLA) during associative learning. Altogether this panel will highlight the functions of anatomically and neurochemically distinct PVT subpopulations in mediating a wide range of motivated behaviors, providing insights into the circuit- and cellular-based mechanisms in psychiatric disorders.

PANEL • SUNDAY • 4:30 PM – 6:30 PM • WASATCH A

Contributions of Locus Coeruleus Dysfunction to Neurodegenerative Disorders

Chairs: Michael Kelberman, Alexa Iannitelli
Presenters: Qi Yuan, Michael Kelberman, Neus Falgàs, Claire O'Callaghan

The locus coeruleus (LC) is the brain's primary noradrenergic nucleus, Pand evidence of LC dysfunction and degeneration in neurodegenerative disorders is well documented. The LC experiences early accumulation of disease-specific aggregates (tau in Alzheimer's disease and alpha-synuclein in Parkinson's disease) which are temporally linked with comorbid neuropsychiatric symptoms (sleep disturbances, changes in mood, stress/anxiety) that predate primary symptomology (cognitive deficits and motor impairments in Alzheimer's and Parkinson's disease, respectively). In later stages of disease, the LC suffers catastrophic cell loss, while preservation of LC integrity is associated with better clinical outcomes. The LC also engages compensatory mechanisms during disease progression in response to pathological insults, such as axonal sprouting, receptor hypersensitivity, and altered firing rates/patterns that may contribute to early behavioral manifestations. Thus, noradrenergic dysfunction is a near ubiquitous feature at every stage of the most prevalent neurodegenerative disorders.
This panel will be led by Michael Kelberman and Alexa Iannitelli (PhD Candidates, Neuroscience Graduate Program, Emory University, Weinshenker Lab). The panel will commence with Dr. Qi Yuan presenting preclinical data on the effects of pretangle human tau and LC activity patterns on overall neuronal health in rats. Next, Michael Kelberman will discuss how hyperphosphorylated tau affects LC neuron firing rates, and how correcting these firing patterns can improve brain-wide functional connectivity in a transgenic rat model of Alzheimer's disease. Dr. Neus Falgàs will follow with a talk on LC degeneration in Alzheimer's disease variants and its contribution to the development of sleep disturbances. Dr. Claire O'Callaghan will close the session considering the use of LC imaging to stratify patients for noradrenergic-based interventions to treat neuropsychiatric symptoms in Parkinson's disease.

PANEL • SUNDAY • 4:30 PM – 6:30 PM • WASATCH B

Transformative Gene Therapy Strategies for Disorders of the Brain and Spinal Cord

Chair: Isabelle Aubert
Presenters: Cassandra Dennys-Rivers, Rikke Hahn Kofoed, Kathrin Meyer

Cutting-edge technologies are being developed to bring safe and non-invasive gene therapies to the clinic for the long-term treatment of disorders affecting the central nervous system. Dr. Dennys will discuss advances and novel thought processes in the fields of capsid evolution and delivery to the brain and spinal cord for recombinant adeno-associated viruses (AAVs). Dr. Kofoed will introduce the use of MRI-guided focused ultrasound combined with intravenous microbubbles (MRIgFUS) to non-invasively increase the permeability of the blood-brain barrier (BBB) and deliver AAV serotypes, e.g., AAV9 and the engineered AAV2-HBKO, administered in the bloodstream to selected brain areas. A brief and localized modulation of the BBB using transcranial MRIgFUS can safely and precisely target brain structures, including deep brain areas that are traditionally difficult to reach. Compared to AAV9, intravenously injected AAV2-HBKO combined with MRIgFUS led to neuronal gene delivery to larger brain regions. Dr. Meyer will present state-of-the-art gene therapy research programs (Rett Syndrome, SMARD1/CMT2S, Batten Disease) and discuss challenges and requirements for translation to clinical trials including the critical steps of optimizing and evaluating gene delivery, treatment efficacy and safety. Dr. Aubert (Chair) will conclude the session and invite the audience and panelists to comment on past, current and future gene therapy strategies that can be lifesaving for patients with cancer, genetic abnormalities, neurodegenerative and neuromuscular disorders of the brain and spinal cord.

BRAIN TALK TOWN HALL

SPECIAL SESSION • 7:00 PM – 8:30 PM • BALLROOM I

JEDI Guardians: Using Neuroscience Knowledge to Promote and Protect Justice, Equity, Diversity, and Inclusion in Schools, Companies, and Communities

Chair: Kyle Frantz
Presenters: Elizabeth Phelps, Laura O'Dell, Stefano Cataldi

Join neuroscientists from around the nation in a discussion about how the brain can both create and resolve racial tensions in our communities. From a biological perspective, there's nothing wrong with creating categories in our minds, noting similarities and differences in the world around us, and using them to decide whether to approach or avoid certain people, places, and things. Similarly, it's often necessary for our survival to act on impulse, use reflexive responses, or make quick decisions based on past experiences. But society goes awry when categories become stereotypes and impulses become racism, sexism, ageism, and other prejudices.

This exciting evening discussion will start by exploring some fascinating research on how human brains process our recognition of social groups that are defined by race. The results suggest that our subconscious (often negative) attitudes about people from different races are usually seated in a brain region associated with fear, whereas our conscious attitudes (often more positive) are centered in brain regions for self-control. Next the panel will consider possible strategies to diminish the activation of fear-regions, for example by interacting regularly with diverse groups of people, celebrating the uniqueness of individuals in our communities, and highlighting the brilliant achievements of historical figures and current leaders from various backgrounds in our nation and around the world. Our Brain Talk Panelists will field questions about this research, how it applies to welcoming students from all backgrounds into science and other fields of study, and how we can translate the ideas into improvements in our workplaces and communities. Audience participation will make this event most enlightening, so come and express your curiosity with us.

Monday, January 23, 2023

MONDAY MORNING PANELS

PANEL • MONDAY • 7:30 AM – 9:30 AM • BALLROOM I

Basal Ganglia Circuit Dysfunction in Parkinson's Disease

Chair: Chris Ford

Presenters: Nicolas Tritsch, Chris Ford, Alexandra Nelson, Thomas Hnasko

Neurodegeneration of SNc dopamine neurons and their forebrain projections is a defining feature of Parkinson's Disease (PD). The resulting loss of dopamine signaling drives multiple alterations within basal ganglia circuits. In this panel speakers will discuss recent work examining the molecular, cellular and circuit mechanisms by which degeneration of dopamine neurons contributes to the dysfunction in striatal circuits and the associated impact of these changes. Nicolas Tritsch (NYU) will discuss recent attempts to dissect the mechanisms responsible for rendering dSPNs abnormally hypersensitive to DA when dopaminergic axons progressively degenerate past a certain threshold in a mouse model of PD. Chris Ford (UC) will discuss recent findings examining how degeneration of dopamine inputs alters cholinergic striatal transmission to D1-MSNs, and potential contribution of this dysfunction to motor impairment. Alexandra Nelson (UCSF) will present on abnormalities of striatal circuit function that correlate with altered decision-making in a new mouse model of Impulse Control Disorder, a complication of PD. Tom Hnasko (UCSD) will describe recent studies showing how genetically defined SN neurons, including VGLUT2-positive DA neurons, can be functionally distinguished and are pathologically resilient to DA neurodegeneration.

PANEL • MONDAY • 7:30 AM – 9:30 AM • MAGPIE A

Auditory System: From Cell Diversity to Behavior

Chairs: Alfonso Junior Apicella, Li Zhang
Presenters: Li Zhang, Patrick Kanold, Robert Liu, Ramnarayan Ramachandran

The panel will focus on discussing the latest progress in elucidating how the transformation of the meaning of an auditory signal to an appropriate behavioral output is achieved by the dynamic interaction of specific neural circuits through different cell types. Here, the panel will cover a few representative research topics, including the modulation of auditory processing by long-range cortical projections, the role of various corticofugal projections in auditory behaviors and how behaviorally-relevant sensory signals are encoded by specific cell types in the auditory system, and what factors might lead to plastic changes.

First, Dr. Apicella will present evidence for layer 4 cortico-striatal projections in the cortical circuit and discuss their roles in physiological and behavioral conditions.

Second, Dr. Zhang will talk about a study on the medium septum and dorsal pontine circuits and will highlight how the negative valence of sound is coded and trans-formed in the central auditory system.

Third, Dr. Kanold will discuss the effects of early sound and visual experience on developing auditory cortex circuits and function.

Fourth, Dr. Liu will talk about how mice learn that a novel sound serves a similar role as a natural vocalization in efficiently guiding animals to perform an innate social behavior.

Fifth, Dr. Ramnarayan Ramachandran will discuss temporal integration in both detection and discrimination behaviors in subcortical auditory centers.

The panel will further discuss recent studies on the functional roles of cell diversity, led by two organizers (Drs Apicella and Zhang). Together, these presentations will provide a diversified view of current research approaches to understanding the functional contributions of the auditory system.

PANEL • MONDAY • 7:30 AM – 9:30 AM • MAGPIE B

Consciousness and Unconsciousness in People and Animals

Chair: Ken Solt

Presenters: Ken Solt, Anthony Hudetz, Kathleen Vincent

Our panel will discuss the neurophysiology of brain transitions that underlie the loss and recovery of consciousness with general anesthesia. Ken Solt will introduce the topic and speak about how our understanding of anesthetic mechanisms has evolved over the years. He will discuss recent work suggesting that midbrain GABAergic neurons play an important role in anesthetic-induced unconsciousness. Tony Hudetz (our Gold Medal Skier) will explain how moments of awareness during anesthesia may come about. He will talk about general anesthesia as a dynamic non-stationary state in humans and animals and the paradoxical spontaneous emergence found by unit recordings in rodents. Kathleen Vincent will describe the role of the mesencephalon in modulating consciousness. She will discuss her work using electric stimulation of the VTA to induce emergence from general anesthesia. She will also talk about recent work employing DREADDs activation of dopaminergic VTA neurons to accelerate the recovery of neurocognitive function after anesthesia using a rodent touchscreen testing paradigm. This panel will provide up-to-date information about the most intriguing mystery in neuroscience, our own consciousness.

PANEL • MONDAY • 7:30 AM – 9:30 AM • PRIMROSE A

Exploring the Neurophysiological Effects of Potentially Therapeutic Psychedelic Compounds

Chairs: Gavin Schmitz, Melissa Herman

Presenters: Alfred Kaye, Gavin Schmitz, William Wetsel, Melissa Herman

Psychedelic drugs are characterized as psychoactive compounds or enactogens that induce changes in cognition, emotion, and perception. These drugs are being investigated as potential therapeutics for many neuropsychiatric disorders including depression, anxiety, and addiction. Despite promising clinical findings, the underlying signaling mechanisms and brain region-specific effects of potentially therapeutic psychedelic drugs remain unclear. This panel will explore the neurophysiological effects of psychedelics on specific brain regions, signaling pathways, and disease-relevant behaviors in preclinical animal

models. Dr. Alfred Kaye (Yale University) will discuss new work exploring the differential effects of entactogens on prefrontal plasticity in fear extinction using optical neurophysiology approaches. Dr. Melissa Herman (University of North Carolina, Chapel Hill) will present new work on the effects of the psychedelic drug psilocin on central amygdala activity. Gavin Schmitz (University of North Carolina, Chapel Hill) will present studies investigating the effects of psychedelic compounds on 5-HT2A serotonergic neurons in the prefrontal cortex of mice, including neuronal firing, receptor involvement, and intracellular signaling pathways. Dr. William Wetsel (Duke University) will present work investigating differences in β-arrestin versus G protein biased signaling at 5-HT2A serotonin receptors and their downstream effects on mouse behaviors. With the escalating interest in the therapeutic potential of psychedelic compounds, more rigorous investigations into the cellular and behavioral substrates of these compounds and their relation to clinical effects are warranted. This panel will present new work highlighting recent advances in our understanding of the neurobiological mechanisms mediating the behavioral effects of psychedelic drugs.

PANEL • MONDAY • 7:30 AM – 9:30 AM • PRIMROSE B

Neural Circuit Mechanisms Underlying the Motivational Control of Behavior

Chair: Sarah Stern

Presenters: Robert Froemke, Dhananjay Bambah-Mukku, Estefania Azevedo, Sarah Stern

Complex motivated behaviors (e.g., mating, parenting, eating and drinking) are necessary for survival of a species, and are thus highly stereotyped. However, the coordination of these behaviors is also modulated by changes in the environment, and dysregulation of these systems may underlie a variety of neuropsychiatric disorders. In this panel, we will therefore explore the underlying neural mechanisms of a variety of motivated behaviors, using cutting-edge techniques. Dhananjay Bambah-Mukku will share his discovery of a sexually dimorphic hypothalamic circuit gating behavioral sex specificity. Robert Froemke will discuss mouse maternal behaviors identified by 24/7 continuous monitoring and the corresponding activity of oxytocin neurons during social interaction, maternal experience, and childcare. Estefania Azevedo will present new work identifying a cell-type specific

neuronal population in the lateral septum that responds to innate and artificial predators and drives food suppression. Lastly, Sarah Stern will describe how internal states are represented in the insular cortex and integrated in a circuit that alters non-homeostatic food consumption. Taken together, this session will detail converging evidence for how complex behaviors are encoded in the brain, and will identify common elements that may be useful in the context of developing mental health treatments.

PANEL • MONDAY • 7:30 AM – 9:30 AM • SUPERIOR

Getting Motivated During Stressful Times Throughout the Lifespan

Chairs: Debra Bangasser, Jared Young
Presenters: Jared Young, Amelia Cuarenta, Deena Walker, Zoe McElligott

There is a wide range of motivation for people to engage in activities, from amotivated states in people with depression and schizophrenia, to hypermotivated states for people with substance use disorders and bipolar disorder. It is critical to determine the underlying mechanisms of motivated behaviors to develop targeted therapeutics for such disorders. One ubiquitous exogenous impact that interacts with disorders is stress. This panel will present findings on the interactions between stress and motivated behaviors relevant to mental health across the life-span and sexes. Dr. Jared Young will present their research determining that both gestation and adult exposure to winter-like short-active photoperiods in adult mice result in amotivated behaviors across sexes. The mechanism(s) underlying these effects are described, including the relationship between altered sleep and neuroinflammation. Dr. Amelia Cuarenta will discuss the effects early resource scarcity on addiction-related behaviors. Her research focuses on the lasting effects of this stressor on opioid and stimulate seeking and relapse behavior, as well as underlying neural mechanisms in rats. Dr. Deena Walker will discuss how adolescent social stress reprograms transcription within the reward circuitry to influence cocaine sensitivity in adult males and females. Her lab explores how nuclear hormone receptors influence transcriptional profiles to induce long-term behavioral changes in motivation across the sexes. Dr. Zoe McElligott will discuss her laboratory's investigations on stress systems in adults under the context of opioid experience and

withdrawal. Specifically, her lab determines how opioids shape the physiology of noradrenergic systems, and how this experience may lead to altered behavioral outcomes. Together the panel will highlight factors that increase vulnerability and resilience to altered motivation and reveal novel mechanisms that may help guide treatment.

PANEL • MONDAY • 7:30 AM – 9:30 AM • WASATCH A

The Effects of Social Interaction and Exercise on SUD-Related Behaviors and Associated Neurobiology

Chairs: Jennifer Wenzel, Natalie Zlebnik
Presenters: Mark Smith, Jonathan Chow, Margaret Rice, Natalie Zlebnik

Substance use disorders (SUD) develop as a result of complex interactions between the environment, the subject, and the drug of abuse. Preclinical research investigating each of these components of SUD has resulted in advancements in our fundamental knowledge regarding the progression from recreational drug use to SUD and severe drug addiction and the underlying behavioral and neurobiological mechanisms. Recently, novel animal models of drug use have increased interest in how enriching the environment with alternative reinforcers, such as a social partner, food, or exercise, may decrease drug intake and drug-seeking behavior. This panel will highlight new research on the role of non-drug reinforcers to influence drug reinforcement and related neurobiology. Mark Smith will discuss how concurrent access to cocaine and a social partner influences the demand for each alternative under free-operant conditions in which responding maintained by each reinforcer was independent and nonexclusive of the other. Jonathan Chow will present data pertaining to dopamine signals during operant social interaction, as well as choice between social interaction and remifentanil. Margaret Rice will discuss work from her lab on the role of BDNF in the effects of voluntary exercise on striatal dopamine release dynamics in mice. Natalie Zlebnik will present work on the effects of voluntary exercise on cocaine-seeking behaviors and cocaine-evoked striatal dopamine release. Altogether, these talks will provide an overview of our current knowledge on the role that environmental influences play in addiction-related behaviors and highlight relevant neurobiology that may provide new avenues for therapeutic investigation.

PANEL • MONDAY • 7:30 AM – 9:30 AM • WASATCH B

From Bunny Slope to Black Diamond: Expert Perspectives on Community Outreach to Enhance Stem Education

Chairs: Michael Stefanik, Patrice Darby
Presenters: Karagh Brummond, Dominique Duncan, Christopher Evans, Amanda Roberts

Collaboration across educational systems is an effective way of creating and maintaining a robust pipeline for tomorrow's STEM leaders. It also inspires the next generation of scientists and are a tool to address inequities in education and STEM success in underrepresented groups. How do we get partnerships and outreach programs to get younger students learning from and interacting with scientists at the forefront of STEM research fields? Karagh Brummond will present her work leading the Science Initiative Outreach Program at the University of Wyoming (UW). This team of faculty and students travel throughout the state facilitating hands-on STEM learning in K-12 classrooms using active learning techniques, integrating experiences into curricula, and creating links between UW and schools in the state. Dominique Duncan will discuss a partnership between USC and neighboring Bravo Medical Magnet High School to involve students and teachers in neuroscience and artificial intelligence research using virtual reality tools. Christopher Evans will discuss DOPA, a high school outreach active-learning program focused on drugs. DOPA is led by senior undergraduate students and taken as a capstone project after didactic courses in pedagogy and addiction neurobiology. The course provides rich experiences for UCLA undergraduate students and survey results of suggest a positive impact. Amanda Roberts focuses on her efforts as PI of the Scripps Research Alcohol Research Center's Dissemination Core to attract under-represented in STEM high school students to biomedical science using a combined virtual and in-person internship approach, graduate and post-doctoral trainee mentorship, and social media. Patrice Darby concludes with about her work as the Program Coordinator at the Meyerhoff Scholar's program at the UMBC to address underrepresentation of African-American researchers and professionals in STEM and provide a path into academic research for students from underrepresented groups.

PIONEER SESSION #2

9:15 AM - 11:15 AM • SUPERIOR

Ventral Tegmental Area Neuronal Diversity, Connectivity, Unanticipated Types of Neurotransmission and Behavior

Pioneer: Marisela Morales
Chair: Elyssa Margolis
Investigators: David Barker, David Root

The goal of Dr. Morales group is to identify the molecules, cells, and neuronal pathways within the reward and stress systems to gain insights into the neurobiology of drug addiction within these systems. She will talk about her journey from identification of different types of neurons within Ventral Tegmental Area (VTA) leading to the discovery of unanticipated forms of neurotransmission and the role of diverse VTA neuronal connectivity in behavior. For two decades, Dr. Morales has been testing the hypothesis that the different roles ascribed to VTA are mediated by distinct subsets of neurons that through specific circuitry integrate information from specific neurons from different brain areas. VTA is best known for having dopamine neurons, but since 2007, Dr. Morales have been providing evidence for the existence of glutamate neurons in the VTA, glutamate neurons that project in parallel to many of the same targets as the dopamine neurons, and her group have begun to determine the role of VTA glutamatergic neurons in behavior. Her group has identified VTA neurons that co-release dopamine and glutamate or co-release glutamate and GABA. She will present evidence indicating that glutamate-GABA neurons have compartmentalize vesicles for the release of GABA or glutamate. In addition to the VTA, Dr. Morales has discovered that a subset of Dorsal Raphe (DR) serotonergic neurons projecting to the VTA co-release glutamate. Almost 20 years ago, in a WCBR session organized by Dr. Kathryn Commons, Dr. Morales presented data showing for the first time that DR serotonergic neurons expressing vesicular glutamate transporter type 3 (VGluT3) release glutamate in VTA and induced reward. At that time, the glutamatergic nature of VGluT3-serotonergic neurons was very controversial, and while the findings presented by Dr. Morales were found exciting by WCBR meeting participants, the manuscript was rejected by peer reviewers for years, and finally published in 2019.

PROFESSIONAL DEVELOPMENT SESSION #2

2:00 PM – 3:00 PM • MAGPIE B

Mid-Career Transitions

Chair: Erik Carlson

Participants: Lloyd Fricker, John Neumaier, David Devilbiss, Kyle Frantz

This is an education panel, chaired by Erik Carlson, and focused on Mid-Career Transitions. Lloyd Fricker will cover Research to teaching. John Neumaier will address transitioning from Clinician/Scientist, academia to government. David Devilbiss will give perspective to transitioning from academia to industry. Kyle Frantz will discuss transitions from research to academia administration.

MONDAY AFTERNOON PANELS

PANEL • MONDAY • 4:30 PM – 6:30 PM • BALLROOM I

Molecule Monitoring in the Study of Substance Use Disorders

Chairs: Suzanne Nolan, Snigdha Mukerjee

Presenters: Leslie Sombers, Suzanne Nolan, Jordan Yorgason, David Lovinger

A majority of the recent work in the study of substance use disorders (SUDs) has utilized high-resolution imaging strategies to gain insight into the time course of cellular mechanisms that are responsible for dysfunctional neurotransmission underlying SUDS, as well as other disorders. With the advent of novel optical sensors in combination with innovations in existing techniques that push the boundaries of their capabilities, it is now possible to monitor the development of dysfunction in neuropsychiatric models with both high spatial and temporal precision. This panel seeks to present data that encompasses novel combinations of existing tools for monitoring a variety of neurotransmitters thereby exploring questions that were previously unanswerable. First, Dr. Leslie Sombers (North Carolina State University) will open our symposium with simultaneous voltammetric measurements of catecholamine and enkephalin dynamics collected in rat striatal slices, adrenal tissue slices, and single chromaffin cells. Second, Dr. Suzanne Nolan (Vanderbilt University, co-chair) will provide data revealing novel insights into the spatiotemporal dynamics of primate prefrontal cortex using a combination of calcium sensors

and genetically encoded sensors. Next, Dr. Jordan Yorgason (Brigham Young University) will present data outlining a novel imaging technique that allows for label-free structural imaging co-registered with labeled imaging at submicron resolution. Finally, Dr. David Lovinger (NIH) will close our symposium with exciting new work exploring the production and release of endocannabinoids using novel genetically encoded sensors. Together, these data will highlight the diversity and flexibility of various ex vivo recording techniques and illustrate how these tools can be leveraged to afford novel insights into both the structure and function of neurotransmitter systems during disease states as well as further understanding of basic physiological mechanisms.

PANEL • MONDAY • 4:30 PM – 6:30 PM • MAGPIE A

Perception to Action: Processing Sensory Signals in Complex Environments

Chair: Sandra Kuhlman

Presenters: Sandra Kuhlman, Renata Batista-Brito, Michael Goard, Huizhong Tao

During postnatal development mammals gain independence as they expand their behavioral repertoire. New skills and behaviors continue to be learned well into adulthood. Adult learning is essential for navigating complex environments and executing high performance maneuvers in natural settings. Precisely how new information is integrated into existing networks is an active area of research, both experimentally and in the field of artificial intelligence (AI). In this panel we will explore the process by which neural circuits develop the ability to encode salient cues in complex environments. Strategies to rescue contextual-cue processing deficits in adults will be discussed. First we will consider the extent to which adult learning and the encoding of complex stimuli disrupts or is otherwise constrained by previously acquired skills and functionality. Next, experiments detailing the impact that disruption of genes associated with neurodevelopmental disease have on perception during the transition to independence will be presented. This will be followed by a discussion of how visual landmarks are used to anchor internal representations of heading direction to the local environment, a process that facilitates navigation in healthy adults.
The panel will conclude with a presentation describing how salient, reward-predicting cues transform sensory-driven responses to promote

appetitive learning and behavioral adaptation to local conditions of how visual landmarks are used to anchor internal representations of heading direction to the local environment, a process that facilitates navigation in healthy adults. The panel will conclude with a presentation describing how salient, reward-predicting cues transform sensory-driven responses to promote appetitive learning and behavioral adaptation to local conditions.

PANEL • MONDAY • 4:30 PM – 6:30 PM • MAGPIE B

Cell-Type Specific and Activity Dependent Transcription Regulation in Cocaine-Activated Ensembles

Chairs: Marine Salery, Philipp Mews

Presenters: Katherine Savell, Kimberly Thibeault, Marine Salery, Philipp Mews

Pathological drug-seeking and the lasting risk of relapse that characterize addiction result from persistent genetic and epigenetic adaptations in the brain circuits involved in reward learning. Neuronal activity in these circuits mediate behavior and the ability to update information in real-time. Across cell types, the activation level of individual cells can be used to further segregate neuronal ensembles selectively recruited by drugs. This panel will present emerging data converging on the notion that activity-related transcriptional and epigenetic processes arbitrate the stabilization of new information and learned behaviors. Katherine Savell (NIDA IRP) will describe the transcriptional fingerprint of cue-induced cocaine seeking ensemble neurons in infralimbic cortex of Fos-mRFP transgenic rats using FACS-purified Fos neurons and snRNA-seq, including cell types and transcriptional profiles of these cocaine-relapse neurons. Kimberly Thibeault (Vanderbilt U) will show how the use of transgenic animals allows for temporally specific tagging of ensembles to record from, identify, and manipulate neurons that are selectively activated by cocaine experience. She will discuss their precise role in cocaine associated behaviors and how they are altered by repeated experience. Marine Salery (Mount Sinai) will describe the dynamics of reactivation of cocaine-recruited ensembles in the in nucleus accumbens of Arc-CreERT2 mice in cocaine-context memory, using snRNA-seq experiments to survey transcriptomic profiles of the reactivated ensembles. Philipp Mews (Mount Sinai) will discuss the role of neuron subtype-specific chromatin remodeling in nucleus accumbens for long-lasting

drug-induced changes in gene regulation, circuit connectivity, and behavior. Together, this session will showcase how circuit activity and neuro-epigenetic remodeling cooperate to shape behavior, knowledge of which will ultimately pave the way towards novel therapeutics for neuropsychiatric disorders.

PANEL • MONDAY • 4:30 PM – 6:30 PM • PRIMROSE A

Stress and Trauma Effects on Motivated Behavior

Chair: Nick Hollon

Presenters: Lauren Burgeno, Matthew Wanat, Abigail Schindler, Christopher Olsen

Stress and traumatic brain injury can have profound impacts spanning reward-seeking behavior, impulsivity, and substance use. Alterations in multiple neuromodulatory systems including striatal dopamine and acetylcholine signaling may underlie these effects. Lauren Burgeno (University of Oxford) will discuss how striatal acetylcholine in the nucleus accumbens and dorsomedial striatum differentially contribute to cue-guided, flexible decision making by signaling unexpected changes in the environment. Matt Wanat (University of Texas at San Antonio) will discuss how acute and repeated exposure to prior stress impacts behavioral responding to reward-predictive cues and dopamine release during Pavlovian conditioning. The stress-related signals meditating these behavioral effects and sex differences will also be discussed. Abigail Schindler (V.A. Puget Sound Health Care System / University of Washington) will describe the effects of repetitive blast polytrauma on mesolimbic dopamine transmission and behavioral flexibility. They have found that repetitive blast exposure in male mice results in disparate effects in relation to tonic and phasic dopamine release patterns and maladaptive changes in appetitive motivation, behavioral flexibility, and impulsivity. Chris Olsen (Medical College of Wisconsin) will talk about the impact of chronic neuropathic pain on oxycodone seeking. Behavioral effects will be discussed in the context of neuroadaptations in prefrontal drug-seeking ensemble and non-ensemble neurons. As chair, Nick Hollon (University of California San Diego) will provide introductory comments and lead discussion of the presentations.

PANEL • MONDAY • 4:30 PM – 6:30 PM • PRIMROSE B

Neuronal Heterogeneity of the Dorsal Raphe and its Role in Motivated Behaviors

Chairs: Marisela Morales, Flavia Barbano

Presenters: John Neumaier, David Prober, Mitchell Spring, Flavia Barbano

The dorsal raphe nucleus (DR) has been classically identified as the major source of the neurotransmitter serotonin. Several decades of research have characterized the role of the DR in the processing of emotions, stress, anxiety, and depression. In addition, the DR also plays a role in salience encoding and reward; and many of these functions have been attributed to the serotonin system arising from it. However, the DR is a heterogeneous structure comprised of diverse neuronal subpopulations that include serotonergic, glutamatergic, GABAergic, and dopaminergic neurons. The panel will discuss the role played by different DR neuronal subpopulations in motivated behaviors. Dr. John Neumaier (University of Washington, Seattle) will present findings on sequency of serotonergic neuron, stress-induced changes in gene expression and the role of circulating stress hormones and DR serotonergic regulation of stress responses. Dr. David Prober (California Institute of Technology, California) will discuss how serotonergic neurons modulate sleep in zebrafish and mice, highlighting an evolutionary conserved mechanism for sleep homeostasis. Dr. Mitchell Spring (Dartmouth College) will present work using the GRAB-5-HT sensor to monitor serotonin release in the dorsomedial striatum during reward anticipation, consumption, and goal-directed actions. Dr. Flavia Barbano (National Institute on Drug Abuse, Baltimore) will discuss the role of DR glutamatergic or serotonergic projections to the Ventral Tegmental Area in cocaine-seeking behavior. The scientific interest and novelty of the findings to be presented at the panel reside in the unexpected roles that different neuronal subpopulations of the DR are playing. Our panel highlights this diversity and integrates findings that ultimately will help to clarify the DR function based on its neuronal diversity.

PANEL • MONDAY • 4:30 PM – 6:30 PM • SUPERIOR

Pain Neurocircuits: Nociception, Affect and Opioid Seeking

Chair: Nicolas Massaly

Presenters: Yarimar Carrasquillo, Jessica Wojick, Nicolas Massaly, Jose Moron-Concepcion

In this panel we will discuss recent findings investigating pain-induced alterations in neurocircuits underlying allodynia/hyperalgesia, negative affective states and opioid seeking/consumption. Dr. Carrasquillo (NIH) will discuss the evidence from her laboratory showing that the CeA functions as a pain rheostat system that can amplify and suppress pain in a cell-type-specific manner. She will also present the results of follow up experiments that delineate cellular and circuit mechanisms underlying the dual and opposite function of the CeA in pain modulation.
Mrs Wojick (University of Pennsylvania) will discuss how nociceptive Rspo2+ neurons within the basolateral amygdala (BLA) are essential to pain aversion and protective behavior. She will also present characterization of BLA calcium activity across acute and chronic pain states BLA activation sufficiency to produce nociception and negative affect in uninjured mice. Lastly, she will present new BLA axon-calcium imaging in a nociceptive subregion of the nucleus accumbens shell expressing Drd2 and Oprk1 that is stable across pain states.
Dr Massaly (University of California, Los Angeles) will present recent findings on pain-induced alterations on dynorphin projections to the lateral hypothalamus. Furthermore, he will elaborate on their activity during noxious vs non-noxious stimuli in pain and physiological states as well as discuss their necessity and sufficiency to drive pain-induced negative affect.
Lastly, Dr Moron-Concepcion (Washington University) will present new findings on the role of VTA dopamine (DA) neurons on pain-induced anhedonia-like behavior. More specifically, he will present how pain enhances the inhibitory drive from the rostral tegmental area (RMTg) to the VTA resulting in decrease DA cell function which subsequently 1) acts to impact motivated behavior and 2) facilitates the intake of the highly abused opioid, fentanyl, in a sex- and time-dependent manner.

PANEL • MONDAY • 4:30 PM – 6:30 PM • WASATCH A

Postsynaptic Signaling at Glutamatergic Synapses

Chair: Johannes Hell

Presenters: Johannes Hell, Weifeng Xu, Andres Maricq, Mark Dell'Acqua

The majority of synapses in the brain are glutamatergic. AMPA-type glutamate receptors (AMPARs) mediate most of the excitatory glutamatergic synaptic transmission under basal conditions and their dysfunction has been implicated in a number of brain disorders. Johannes Hell will chair this panel and introduce the general topic. Hell will then discuss aspects of the regulation of AMPAR trafficking by norepinephrine including intracellular signalling by NE and the role of the L-type channel Cav1.2. Weifeng Xu will illuminate how the calmodulin (CaM) binding protein neurogranin recruits apoCaM to the postsynapse and how this affects regulation of postsynaptic glutamate receptors. Maricq will describe the regulation and function of glutamate receptors C. elegans. Dell'Acqua will describe how L-type voltage-gated Ca2+ channels control postsynaptic structural plasticity through bi-directional signaling interactions with and long-term remodeling of the dendritic spine endoplasmic reticulum.

PANEL • MONDAY • 4:30 PM – 6:30 PM • WASATCH B

New Kid on the Appetite Block: Regulation of Ingestive Behaviors by the Parasubthalamic Nucleus

Chairs: Candice Contet, Matt Carter

Presenters: Marie Barbier, Matt Carter, Candice Contet, Jiahao Ye

Ingestive behaviors are regulated by a network of appetite-inducing and appetite-suppressing neuronal populations throughout the brain. Recently, a relatively unexplored structure in the posterior lateral hypothalamus, the parasubthalamic nucleus (PSTN), has emerged as a critical player in the regulation of appetite. This panel will present recent findings that reveal the anatomical connectivity and functional properties of distinct PSTN cell types in various ingestive behaviors. Dr. Marie Barbier will present recent work demonstrating that the PSTN and adjacent calbindin nucleus form a complex connected to the central nucleus of the amygdala and insular cortex, which plays a role in the

cognitive and interoceptive gating of feeding behavior. Dr. Matt Carter will then show that the PSTN is composed of multiple cell types, and that cells expressing tachykinin-1 (Tac1) suppress feeding and are necessary for the appetite-suppressing effects of a variety of satiety hormones. Next, Dr. Candice Contet will discuss evidence that the PSTN exerts bidirectional control over alcohol consumption in a cell-type specific manner, with a unique role of Crh-expressing neurons promoting intake. Finally, Dr. Jiahao Ye will share evidence of sensory drives on the neural activity of the PSTN. Taken together, this session will elucidate the role of the PSTN in ingestive behaviors, describing the relevant cell types, anatomical projections, activity patterns, and related behavioral phenotypes. Dr. Carter will introduce the session and Dr. Contet will lead discussion of the presentations.

MONDAY EVENING PANELS

SHORT COURSE • MONDAY • 7:00 PM – 8:30 PM • BALLROOM I

Novel Paradigms and Automated Behavioral Analyses for the Study of Motivation and Addiction

Chair: Jibran Khokhar

Presenters: Yujia Hu, Christie Fowler, Jibran Khokhar

The development and incorporation of new technologies and animal models is essential to progress in behavioral neuroscience. For example, advancements in machine learning, and computer vision have the potential to greatly impact approaches to behavioral analysis, particularly in regard to automated and quantitative measures. Furthermore, several groups are developing new approaches to studying drug self-administration behavior, including using vaporized drug delivery systems and examining social aspects of behavior. The goals of this short course are to introduce new deep-learning based automated approaches to behavioral analysis (LabGym and Deep Animal) and emerging vape drug self-administration procedures to the Winter Brain community. Dr. Jibran Khokhar will begin with a brief introduction and background to some of the challenges of automated behavioral analysis and a brief history of the use of drug-self-administration procedures. Dr. Yujia Hu will then present “LabGym” a newly developed deep-learning based package for classification and quantification of user-defined animal behaviors across species including rats, mice, and flies.

Dr. Christie Fowler will discuss the development of an e-cigarette nicotine self-administration procedure for rats and mice and will highlight considerations for successful implementation of the protocol with chamber design and vape equipment. Finally, Dr. Jibran Khokhar will give an overview of several types of vaping tools used for THC and nicotine vapour exposure and self-administration. He will focus on approaches and considerations for their use including what can be gained from the different types of equipment available, research design considerations (e.g., pharmacokinetics) and research questions that can be addressed. These talks will set the stage for discussion and information-sharing at the end of the session.

SHORT COURSE • MONDAY • 7:00 PM – 8:30 PM • MAGPIE A

A Helicopter-View of the Chutes, Glades, Bowls and Peaks of Clinical Brain Stimulation

Chair: Joshua Brown

Presenters: Tracy Barbour, Darin Dougherty, Nick Trapp

Clinical Brain Stimulation has grown exponentially as a treatment modality in psychiatry and neurology, and translational research in this area is one of the hottest subjects in neuroscience. This short course will give an overview of clinical brain stimulation modalities for non-clinicians and clinicians who do not practice neuromodulation. We will touch on purported mechanisms of action, methods, clinical evidence for efficacy, clinical indications, investigational indications and potential adverse events. Specifically, we will cover electroconvulsive therapy (ECT), transcranial direct current stimulation (TMS), deep brain stimulation (DBS), transcranial direct current stimulation (tDCS). The goal would be for attendees to have familiarity with each modality promoting awareness of the field, and potentially spark collaborative research ideas.

PANEL • MONDAY • 7:00 PM – 8:30 PM • MAGPIE B

Visualizing RNA Dynamics in Living Animals

Chair: Oswald Steward

Presenters: Sulagna Das, Andrej Luptak, Oswald Steward

MRNA localization and local translation in neuronal dendrites has been widely studied in vitro, but knowledge of RNA dynamics, localization and local translation in neurons in living animals is very limited. This panel will discuss novel technologies to fill this information gap. Sulagna Das will report studies using high resolution imaging of endogenous dendritic mRNAs with different half-lives to define dynamics of their synaptic localization and translation upon stimulation. While constitutive, long-lived mRNAs like ß-actin persist in the dendrites and undergo multiple rounds of translation, transcripts with short half-lives like Arc are induced intermittently to supply proteins only in local dendritic hotspots that are maintained over time. The differential regulation of mRNAs in the dendritic space over time may be a mechanism for remodeling of particular spine synapses. Andrej Luptak will report initial development of new bioluminescent technologies to report steps in the life history of mRNAs in living brains. In bioluminescence, the enzyme luciferase operates on substrate luciferin to generate photons with no background, which can be repeatedly imaged over time in living animals. Using the MS2-PP7 stem loop technologies developed initially by Rob Singer's group, the team has engineered unique RNA sequences that recruit different parts of split bioluminescent molecules upon transcription and optimized this system to modularly tag and visualize RNAs in a variety of contexts. These results provide the foundation for visualizing RNA dynamics in living mice. Os Steward will describe initial results deploying this novel bioluminescent technology in living mice using AAVs that are transported retrogradely over long distances to remotely and selectively transduce cortical motoneurons involved in motor learning. The panel will end with a discussion on the advantages and limitations/caveats of the current approaches and potential future directions.

PANEL • MONDAY • 7:00 PM – 8:30 PM • PRIMROSE A

Brain Positron Emission Tomography in Substance Use Disorders: Studies With Pharmacological Challenges

Chair: Corinde Wiers

Presenters: Peter Manza, Ansel Hillmer, Corinde Wiers

Understanding the pathophysiology of substance use disorders and therapeutic developments require a strategy that appreciates systemic effects of substances on the brain. A molecular investigation of the effects of pharmacological challenges on the brain in vivo can be achieved by studies with position emission tomography (PET). With PET research we can identify molecular pathways involved in substance use disorders, explore chronic and acute effects of drugs of abuse on the brain, and test neural mechanisms of new pharmacological treatments. In this symposium the speakers will present breakthrough research findings from recent and ongoing studies to illustrate the utility of a pharmacological challenge approach on brain PET in individuals with substance use disorders.

Dr. Peter Manza will present preliminary evidence that individuals with an opioid use disorder on maintenance drugs do not appear to have deficits in dopamine D2 receptor availability, or in stimulant-induced dopamine increases that have been previously reported in untreated patients with an opioid use disorder.

Dr. Ansel Hillmer will provide evidence that acute oral alcohol exposure in binge drinking individuals increases the brain PET PBR28 binding by 22%, indicative of an acute immune response elicited from an acute oral alcohol challenge.

Dr. Corinde Wiers will present preliminary results on the effects of a ketone ester supplement drink decreasing brain glucose metabolism by 18.5%, as compared to a baseline scan in individuals with Alcohol Use Disorder, consistent with a shift from glucose to ketones as a brain energy source, which may have therapeutic benefits in reducing alcohol withdrawal and alcohol craving.

The symposium brings together early investigator speakers from different institutions in the US who work on PET studies in substance use disorders.

PANEL • MONDAY • 7:00 PM – 8:30 PM • PRIMROSE B

Diverse Model Systems to Interrogate Psychiatric Disorders: Challenges and Opportunities

Chair: Elizabeth Tunbridge

Presenters: Wilfried Haerty, Brady Maher, Thomas Hyde

Historically, the lack of appropriate model systems proved a major barrier to the development of improved treatments for psychiatric disorders. However, over the last decade intellectual and technical advances have provided new tools and insights to develop, understand and refine the model systems needed for such advances. These developments pave the way to identify new pathophysiological mechanisms and to improve model systems for drug development. This panel will outline how the use of complementary model systems enables researchers to integrate information from distinct approaches to better understand the biological mechanisms underlying psychiatric disorders, and ultimately to identify and test novel therapeutic approaches.
Liz Tunbridge (Oxford) will introduce the panel and give an overview of the range of model systems available to psychiatric researchers, and their strengths and weaknesses. Wilfried Haerty (Earlham Institute) will demonstrate how he has used novel technical and analytic approaches to better understand classical model systems, highlighting that, even in the case of well-studied models (including neuroblastoma cells and mice), we still have a lot to learn. Brady Maher (Lieber Institute for Brain Development) will demonstrate how multimodal characterization of patient- and control-derived iPSCs and organoids, stratified based on polygenic risk for schizophrenia, can be used to define molecular and cellular correlates of clinical phenotypes. Finally, Tom Hyde will demonstrate how the application of cutting-edge technical approaches to high-quality postmorten human brain tissue can be used to provide an ever better understanding of the molecular profile of psychiatric disorders.

PANEL • MONDAY • 7:00 PM – 8:30 PM • SUPERIOR

Defensive Survival Mechanisms in Neuroethological Models of Fear

Chair: Annie Ly

Presenters: Annie Ly, Romain Durand-de Cuttoli, Courtney Wilkinson, Dean Mobbs

The field of neuroethology is the study of the neural basis of an animal's innate behavior. Neuroethological models of fear are built upon the premise that animals and humans exist in a risky world that necessitates decision-making based on innate responses to a threat. The field of neuroethology, particularly regarding the underlying defensive response to threats, has expanded substantially with the advent of novel methods of recording neural activity. The proposed panel will present work using neuroethological models of fear and real-time neural correlates to explain changes in decision-making processes. Firstly, Annie Ly (Chair), a 3rd year Ph.D. candidate at the University of Colorado Boulder, will present her work using a foraging behavior paradigm in mice to assess the impact of a robotic or live predatory threat on avoidance behavior, as well as the involvement of the bed nucleus of the stria terminalis (BNST) in threat processing. Next, Dr. Romain Durand-de Cuttoli, who is a post-doctoral fellow at the Icahn School of Medicine at Mount Sinai, will present on how stress-resilient mice optimize subjective value and food security on an economic foraging task. Next, Courtney Wilkinson, a 4th year Ph.D. candidate at the University of Florida, will present work on how the individual vulnerability to predator scent stress enhances oxycodone-seeking in rats. Lastly, Dr. Dean Mobbs from Caltech, who is a Professor of Cognitive Sciences and Director of the Caltech Brain Imaging Center, will conclude the panel by presenting work related to human responses to perceived threats using brain-imaging and computational modeling. The goal of the panel is to present behavioral models that assess how decision-making is impacted by fear while also leveraging modern methods of neuroscience to examine the intrinsic neural circuitry. The work presented by panel presenters will ideally promote a discussion on both the historical and current perspective on neuroscience research of affective states.

PANEL • MONDAY • 7:00 PM – 8:30 PM • WASATCH A

Emerging Issues of Motor Thalamus

Chairs: Jun Ding, John Huguenard
Presenters: Jun Ding, Tianyi Mao, John Huguenard, Kamran Khodakhah

Controlling and coordinating our body's movement and adapting to learn new motor skills are one of the main functions of the brain and are essential for the survival of all animal species evolutionarily and involve multiple brain regions that each modulate specific aspects of the movement. To fully understand how the brain controls movement and how this process is altered in motor diseases such as Parkinson's or ataxia, we need to uncover how these distinct motor-related brain regions together orchestrate their activity. Two of the major brain regions involved in generating and refining motor commands are the basal ganglia (BG) and cerebellum (CB). The outputs of the BG and CB both project to the motor nuclei of the thalamus, which in turn relay motor signals to the cortex. Despite the importance of BG and CB interactions, several technical challenges remain. First, the long-range nature of the BG and CB projections made it difficult to study their interactions. Second, the lack of molecular markers for these projection neurons has limited genetic access to these cells.
In this session, we will discuss the emerging issues of the motor thalamus. First, Dr. Jun Ding (Stanford) will present recent findings on how BG and CB circuits interact in the motor thalamic regions using recently developed trans-synaptic viral labeling technology. Second, Dr. Tianyi Mao (OHSU) will discuss the connectomic approaches to 3D reconstruct images from serial coronal sections of the whole brain and register to the Allen Brain Atlas, which allows precise quantification of innervation of motor thalamus by BG and CB. Third, Dr. John Huguenard (Stanford) will discuss the unique biophysical properties of the motor thalamic neurons, which allow them to integrate excitatory and inhibitory inputs from CB and BG, respectively. Finally, Dr. Kamran Khodakhah (Albert Einstein) will present his work on CB modulation of the motor thalamus and its involvement in movement disorders.

PANEL • MONDAY • 7:00 PM – 8:30 PM • WASATCH B

Alpha -Synuclein Function in Health and Disease

Chair: Hong-yuan Chu

Presenters: Sreeganga Chandra, Jacqueline Burré, Hong-yuan Chu

The presynaptic protein alpha-synuclein (aSyn) expresses widely in the brain and its abnormal aggregation is implicated in the pathogenesis of a group of neurological disorders (i.e., synucleinopathies), including Parkinson's disease. Growing body of evidence suggests that formation of insoluble aggregates causes a reduced level of soluble aSyn and disrupts its normal subcellular distribution, which can be important aspects of disease mechanisms. Thus, there is an unmet need to better understand the normal function of α-synuclein to gain better understanding of the biology of synuceinopathies.

This panel will discuss recent findings in the physiological function of aSyn and how loss of such normal function may lead to circuitry dysfunction. Dr. Sreeganga Chandra will discuss how aSyn regulates synaptic vesicle endocytosis, focusing on its role as an endocytic accessory protein that acts at early stages of synaptic vesicle endocytosis to controls the size and curvature of clathrin structures on the membrane. Dr. Jacqueline Burré will discuss the importance of membrane binding of aSyn for synaptic vesicles and chaperoning of SNARE-complex assembly in both health and diseases. She will also discuss modulators of aSyn binding to synaptic vesicles. Dr. Hong-Yuan Chu will discuss aSyn distribution among glutamatergic axon terminals and the impact of its aggregation on synaptic transmission and plasticity in a mouse model of synucleinopathies. This panel will be of interest to a broad audience from neuroscience and neurology research fields.

Tuesday, January 24, 2023

TUESDAY MORNING PANELS

PANEL • TUESDAY • 7:30 AM – 9:30 AM • BALLROOM I

Immune Signaling Mechanisms of Pathology in Addiction

Chairs: Fulton Crews, A. Leslie Morrow

Presenters: Leon Coleman, Carolina Haass-Koffler, M. Foster Olive, Rajesh Miranda

Neuroimmune signaling is a mechanism of alcohol and stimulant pathologies through new emerging mechanisms that include extracellular vesicles (EVs). In this panel we investigate translational impacts of neuroimmune activation and EV signaling. Speaker 1, (Leon Coleman) will present preclinical findings that proinflammatory signaling caused by alcohol abuse underlies alcohol-related neurodegeneration in the prefrontal cortex (PFC), loss of adult hippocampal neurogenesis, and heighted stress reactivity in vivo. His studies find EVs as fundamental drivers of immune activation and epigenetic reprogramming caused by ethanol. Speaker 2, Dr. Hass-Koffler will present human studies establishing innate immune signals as a hallmark of alcohol use disorder (AUD). She will extend pre-clinical studies suggesting cannabis modulates the innate immune response to alcohol. She will present human studies on the impact of delta-9-tetrahydrocannabinol (THC) on acute alcohol consumption and innate immune signals. Findings have implications for cannabis as a novel pharmacological target to reduce alcohol-induced inflammation. Speaker 3, Foster Olive will talk about methamphetamine, cocaine and neuroinflammation. He will present studies on increased expression of the protease MMP-9 and other innate immune genes and activation of NF-κB within the NAc and PFC. Using viral-mediated knockdown of NF-κB immune signaling blocks cue-induced cocaine-seeking behavior linking immune signaling to stimulant addiction. Speaker 4, Raj Miranda will present studies on alcohol and EV released from neural stem cells. Using mass spectrometric and sequencing approaches ethanol alters EV protein, miRNA and mRNA, that represents a novel mechanism of developmental ethanol exposure. This panels on addiction pathology and innate immune mechanisms provide new information on novel signaling mechanisms.

PANEL • TUESDAY • 7:30 AM – 9:30 AM • MAGPIE A

Parallel Tracks: Developing New Disease Models and New Therapies for the Treatment of Parkinson's Disease

Chair: Anurag Tandon

Presenters: Janelle Drouin-Ouellet, Alvin Joselin, Anurag Tandon, Warren Hirst

Parkinson's disease (PD) is a debilitating neurodegenerative disorder that affects 8-10 million patients worldwide. In the past few years, advances in our understanding of PD genetics and the underlying molecular pathophysiology have led to exciting new disease models to develop and test new treatments. Like twin rockers that improve manoeuverability on powder and groomed trails, these parallel developments underscore the need to combine basic and applied research to develop novel therapeutics that can achieve the holy grail of disease modification. (i) Janelle Drouin-Ouellet (U Montreal) will discuss the use of direct neural reprogramming of patient-derived dermal fibroblasts to investigate the pathophysiology of Parkinson's disease. She will focus on age-related impairment in autophagy and mitochondrial dysfunction and how induced dopaminergic neurons could be used for molecular stratification of idiopathic Parkinson's disease and drug target validation. (ii) Alvin Joselin (U Calgary) speak about LRRK2 and its new role in phagocytosis, and how the LRRK2 G2019S mutation mediates this effect on phagocytosis and its effect on dopaminergic neuron loss. He will also describe a systematic screen of biologically active compounds for inhibitors of phagocytic function employing a novel cell-based high-content screening approach and the implications of this study on familial and, potentially, sporadic forms of PD. (iii) Anurag Tandon (U Toronto) will focus on using gene therapy to express vectorized anti-alpha-synuclein antibody fragments that can that sequester and degrade excess alpha-synuclein in primary neurons and mice, and assess their protection against spreading synucleinopathy. (iv) Warren Hirst (Biogen) will describe the use of genetics to identify and prioritize therapeutic targets for PD. These defined populations will enable precision medicine but, enabled by biomarkers, will also provide the basis to expand into sporadic Parkinson's disease.

PANEL • TUESDAY • 7:30 AM – 9:30 AM • MAGPIE B

Understanding Abnormal Excitability in Autism Spectrum Disorders: Insights From New Models and Approaches

Chair: Vitaly Klyachko

Presenters: Michelle Antoine, Anis Contractor, Vitaly Klyachko, Anubhuti Goel

Neural circuit hyperexcitability and sensory hypersensitivity are hallmarks of autism spectrum disorders (ASD). It has been proposed that abnormal cortical neuron excitability may underlie the symptoms of ASD, but the mechanisms linking cellular, circuit and behavioral deficits have remained elusive. We will discuss recent advances towards understanding excitability in ASD revealed by an array of genetic mouse models, treatment paradigms and behavioral assays. Michelle Antoine will describe how mice haploinsufficient for the Scn2a gene, which encodes the voltage-gated sodium channel Nav1.2, replicate core aspects of ASD, including learning deficits and sensory abnormalities. Increased temperature without the inflammatory aspect of fever can normalize these deficits by reducing abnormal spiking activity in somatosensory pyramidal neurons. Anis Contractor will discuss experiments in a mouse model with an intellectual disability-associated missense mutation in the kainate receptor subunit GluK2. This mutation alters kainate receptor signaling, dendritic excitability and synaptic integration in hippocampal neurons due to down-regulation of SK potassium channels. Vitaly Klyachko will show that circuit hyperexcitability in the hippocampus of the Fragile X (FXS) mouse model arises from a paradoxical hypo-excitability of excitatory mossy cells, caused by upregulation of Kv7 potassium channels. The circuit hyperexcitability results from reduced excitatory drive to local inhibitory interneurons that are preferentially innervated by the mossy cells. Anubhuti Goel will discuss the design of a novel distractor task to examine neural mechanisms that drive sensory hypersensitivity. Auditory distractors impair task performance in humans with FXS and FXS mice. Susceptibility to sensory distractors correlates with disruption in activity of VIP interneurons. Together, these studies may open new directions to understand hyperexcitability in ASD.

PANEL • TUESDAY • 7:30 AM – 9:30 AM • PRIMROSE A

Calorie Dense Energy Sources Reshape the Brain's Motivation Circuits
Chairs: Richard O'Connor, Dan Christoffel
Presenters: Richard O'Connor, Estefania Azevedo, Dan Christoffel, Stacey Gorniak

The emergence of maladaptive behaviors and reward processing is a core feature of a range of neuropsychiatric disorders. Abundant epidemiological evidence supports the idea that the availability of calorically dense, highly palatable foods is a primary driver of our ongoing obesity crisis. Data collected in human and rodent suggests repeated consumption of such foods impart lasting effects on the function of specific brain circuits. Thus, excessive calorie intake from energy dense sources may lead to the emergence of maladaptive behaviors. Targeting such dysregulated signaling cascades may serve as a therapeutic strategy for reversing motivational aberrations linked to a range of psychopathologies including feeding disorders. This panel will present unpublished research characterizing palatable food induced neuroadaptations in the brain's neurocircuitry and the contribution of such changes to the development of a range of behavioral deficits.

Dr. Richard O'Connor (Icahn School of Medicine) will present work highlighting how diet-induced obesity associated restructuring of hypothalamic circuits reshapes food preference and motivation.

Dr. Estefania Azevedo (Medical University of South Carolina) will present data for a cell-type specific hippocampal circuit involved in context-dependent feeding and how its connection to the hypothalamus affects reward approach and foraging.

Dr. Dan Christoffel (University of North Carolina) will present evidence for cell-type and circuit specific adaptations following long-term high fat exposure in the mesolimbic system and how activity of these elements regulate motivation high-fat diet intake.

Stacey Gorniak (University of Houston) will be sharing data on the behavioral manifestation of obesity & metabolic disease and how these behaviors relate to cortical activity changes.

PANEL • TUESDAY • 7:30 AM – 9:30 AM • PRIMROSE B

Neurobiology of Binge Eating and Food 'Addiction': A Translational Perspective

Chairs: Morgan James, Jessica Barson

Presenters: Marc Potenza, Morgan James, Jessica Barson, Samantha Fortin

Eating disorders have the highest mortality of any psychiatric condition; however, the neural basis of these diseases remains poorly understood. Recently, significant attention has been given to the possibility that some types of foods, particularly those high in fat and sugar, might be 'addictive', and thus their excessive consumption may be governed by the same neural systems that control drug abuse. Our panel combines clinical perspectives on this topic with new, unpublished data from preclinical studies examining the neural basis of excessive food consumption.

Our first panelist is Dr. Marc Potenza, who will present results from studies examining binge eating disorder, obesity and 'food addiction' in humans, including with respect to relationships between brain activations, metabolic measures and food craving and neural and clinical correlates of treatment outcomes. We then shift focus to the use of preclinical models and the insights they can provide at a circuit/systems level. Dr. Morgan James will present evidence that binge-like eating in rodents reverses hedonic deficits associated with obesity and promotes behavior reminiscent of 'food addiction' via an orexin-dependent mechanism. Dr. Jessica Barson will discuss her laboratory's work on sex differences in binge-like eating behavior in mice. She will describe how a neuropeptide in the limbic paraventricular thalamus, pituitary adenylate cyclase-activating polypeptide (PACAP), may participate these differences. Finally, Dr. Samantha Fortin will discuss the neuroanatomically distributed nature of central glucagon-like peptide-1 (GLP-1) signaling in the regulation of energy balance. She will present her work which aims to better understand GLP-1's mechanisms of action in classic feeding centers of the brain as well as atypical sites of food intake control.

PANEL • TUESDAY • 7:30 AM – 9:30 AM • SUPERIOR

The In-and Outs of Monoamine Transporters – Traversing Conformational Bias Toward Novel Therapeutics

Chair: Freja Herborg

Presenters: Amy Newman, Freja Herborg, Ali Salahpour, Ulrik Gether

Transporters of monoamines exert tight control over monoaminergic neurotransmission and are key therapeutic targets in the treatment of neuropsychiatric diseases. Moreover, mutations in monoamine transporter genes can by themselves cause or contribute to a spectrum of diseases. Indeed, a number of these disease-associated variants are amenable to pharmacological chaperoning, providing a new therapeutic application for drugs that target monoamine transporters. Interestingly, conformational biases appear to underlie important differences in behavioral and therapeutic effects. In this panel, Amy Newman will begin by discussing the development of atypical dopamine transporter inhibitors that demonstrate conformational bias and the potential to treat substance use disorders (SUD). Next, Freja Herborg will talk about the identification, characterization and pharmacochaperoning of novel rare coding variants in the serotonin transporter in patients with treatment-resistant chronic affective disorders. Ali Salahpour will present a novel in vivo model of dopamine transporter deficiency syndrome and compounds that target the dopamine transporter as potential candidates for treatment. Finally, Ulrik Gether will discuss how inhibitor-based fluorescent tools can be applied to provide insights into the conformational equilibrium of the dopamine transporter and disease-associated mutants and how these conformational changes relate to their nanoscale organization at monoamine release sites.
Summarized, we explore novel avenues for pharmacotherapy targeting monoamine transporters and the implications of conformational biases for synaptic function, pharmacochaperoning and SUD treatment.

PANEL • TUESDAY • 7:30 AM – 9:30 AM • WASATCH A

Enabling Axon Regeneration in the Adult Nervous System

Chairs: Cedric Geoffroy, Alexandra Byrne
Presenters: Alexandra Byrne, Valeria Cavalli, Alyson Fournier, Cedric Geoffroy

After being injured, adult axons in the central nervous system are not capable of regenerating and peripheral axons lose their regenerative ability with increased age, resulting in a permanent loss of function. To identify therapies that enable repair of the adult nervous system, it is necessary to understand the neuron intrinsic and extrinsic mechanisms controlling regeneration. This panel will present new findings obtained from diverse vertebrate and invertebrate models, including rodents, human cells and nematodes.
Alexandra Byrne (University of Massachusetts) uses Caenorhabditis elegans to investigate how the adult nervous system coordinates multiple aspects of the injury response to achieve repair. She will present the finding that TIR-1/SARM1 (Sterile Alpha and TIR Motif Containing 1), a key regulator of axon degeneration, also regulates the seemingly opposite response to injury, axon regeneration.
Valeria Cavalli (Washington University) uses dorsal root ganglia (DRG) neurons to study cell-extrinsic mechanisms driving axon regeneration. She will discuss how the neuronal microenvironment, including satellite glial cells and macrophages, influences axon regeneration. She will also discuss key features of satellite glial cells that are conserved between human and rodent DRGs.
Alyson Fournier (McGill University) will focus on how to regulate gene expression programs to enhance regeneration of damaged axons in the central nervous system. She will present her findings that targeting programs of gene expression through regulation of miRNA expression and polypharmacological approaches are exciting avenues for promoting axon repair.
Cédric Geoffroy (Texas A and M University) will discuss the pathway-specific age-dependent decline in axon growth after spinal cord injury. He will present the impact of mitochondrial function in cortical neurons. Finally, he will introduce a new screen system for discovering drugs promoting neuroprotection and neurite growth in adult neurons.

PANEL • TUESDAY • 7:30 AM – 9:30 AM • WASATCH B

Exploration of Novel Mechanisms of Psychiatric Illness Reveals Metabolic Changes Across Translational Substrates

Chair: Robert McCullumsmith

Presenters: Consuelo Walss-Bass, Margaret Hahn, Sinead O'Donovan, Amy Ramsey

Off-label interventions are now being deployed for diverse psychiatric disorders, with repurposing of drugs approved for metabolic disorders, such as diabetes, as well as dietary modification, such as the keto diet. However, understanding the molecular changes in the brain that underlie these treatments lags far behind. In this panel, we address this challenge, with data from diverse disease substrates focused on understanding metabolic perturbations in severe psychiatric illness. Dr. Walss-Bass will present work that uses an omics approach to identify SGK1 kinase perturbations in schizophrenia; combining postmortem brain and iPSC-derived neurons, showing changes in expression and activity for this kinase which bridges several metabolic pathways. Dr. Hahn will present work on the effects of antipsychotic medications on central regulation of glucose homeostasis. Deploying a physiological model that chemically clamps the pancreas, her findings identify cell- and region-level signaling networks in the hypothalamus regulating peripheral glucose metabolism perturbed by antipsychotics. Dr. O'Donovan will present her work examining the ATPome in MDD and SCZ. Using a cutting-edge approach, changes in ATP-binding proteins (aka the ATPome) were detected in postmortem brain, with different patterns for MDD and SCZ. These data open a new avenue for assessing metabolic changes in brain diseases. Dr. Ramsey will present work in a model of NMDAR dysfunction, which is relevant to schizophrenia, autism, and other brain disorders. Her data show the effects of dietary interventions (keto and BHB) on white matter integrity, mitochondrial function, and cognition. Her findings directly inform the putative restorative mechanisms associated with dietary interventions. In summary, this panel provides a fresh and exciting perspective on metabolic derangements in the brain in psychiatric illness, combining cutting-edge approaches with novel ideas that will help move the field forward.

TUESDAY AFTERNOON PANELS

PANEL • TUESDAY • 4:30 PM – 6:30 PM • BALLROOM I

Striatal and Non-Striatal Dopamine Signaling in Motivated Behaviors, Learning, and Affective States

Chair: Carole Morel

Presenters: Allyson Friedman, Erin Calipari, Arthur Godino, Carole Morel

The dopamine system broadcasts signals throughout the brain, regulating healthy brain functions and adaptive behaviors. However, the neural circuit and cellular mechanisms by which discrete behavioral responses and adaptations are being encoded remain elusive. This panel will review physiological, functional, and behavioral new evidence, establishing the multifaceted role of dopamine, beyond reward processes, in integrating internal states and encoding motivated social behaviors, learning, decision-making, and affective states. First, Dr. Allyson Friedman (CUNY) will detail the cellular mechanisms by which the estrous cycle in female mice regulates midbrain dopamine neuron excitability, activity, and reactivity to environmental stressors and subsequently shapes motivated social behaviors. Dr. Erin Calipari (Vanderbilt University) will then describe how dopamine in the nucleus accumbens core evoked by novel, neutral stimuli mediates latent inhibition. She will show that optogenetic manipulation of dopamine during cue habituation bidirectionally influences future associative learning, revealing the causal role of striatal dopamine in novelty-based learning. Arthur Godino, from Dr. E. Nestler lab (Mount Sinai), will present ongoing studies examining in vivo how dopamine dynamics regulate the ventral hippocampus D1- vs D2-neurons activity, control the representation of emotionally-salient stimuli and, finally, cell-specifically gate or refrain exploratory behaviors. Dr. Carole Morel (Mount Sinai), following up on this work, will describe how midbrain projection to the amygdala encodes social stress-induced anxiety and discuss how alterations of parallel dopamine circuits result in distinct features of chronic stress behavioral outcomes. Collectively this panel will highlight the complexity of the dopamine circuit mechanisms that govern adaptive behaviors and affective states with an emphasis on translational implications and emerging hypotheses.

PANEL • TUESDAY • 4:30 PM – 6:30 PM • MAGPIE A

Serotonin in Learning and Reward

Chairs: Katherine Nautiyal, Mitchell Spring

Presenters: Catia Teixeira, Marisela Morales, Mitchell Spring, Katherine Nautiyal

The role of serotonin in behavioral neuroscience has often been studied in the context of anxiety and depression, with motivation and learning more strongly linked to dopamine. However, it has become clear in recent years that serotonin is also involved in reward-related behaviors, both through interactions with the dopamine system and through dopamine-independent mechanisms. This panel will discuss the role of serotonin in encoding and modulating reward-related behaviors. Dr. Kate Nautiyal (Dartmouth College) will chair the session and provide introductory remarks. Dr. Catia Teixeira (Nathan Kline Institute) will discuss how early life environmental factors regulate serotonergic-dopaminergic interactions and influence adult behavior. Pharmacological or genetic manipulations leading to elevated serotonin levels in developing mice alter dorsal raphe inputs to the ventral tegmental area, which is implicated in altered exploratory behavior in adulthood. Dr. Marisela Morales (NIDA) will discuss the involvement of dual serotonergic/glutamatergic Dorsal Raphe (DRN) neurons in reward. She has found that glutamate and serotonin release by these neurons in the ventral tegmental area are differentially involved in cocaine and non-drug reward. Dr. Mitch Spring (Dartmouth College), a postdoctoral fellow in the Nautiyal Lab, will present work using GRAB-5-HT sensor to monitor dorsotriatal serotonin release during reward-related behavior. He has found that dorsal striatal serotonin increases during reward pursuit and consumption, and is sensitive to reward value. Finally, Dr. Kate Nautiyal (Dartmouth College) will present additional work from the lab using 1P calcium imaging in the dorsal striatum to measure how serotonin influences the encoding of reward and action in medium spiny neurons in mice. Mice lacking serotonin signaling through the 1B receptor, have decreased inhibition of medium spiny neurons during reward anticipation compared to wildtype controls.

PANEL • TUESDAY • 4:30 PM – 6:30 PM • MAGPIE B

Recent Advances in Epileptology: Seizure Detection, Neuroimaging and Status Epilepticus

Chair: Olaf Paulson

Presenters: Claude Wasterlain, Sándor Beniczky, Lars H. Pinborg, Olaf Paulson

Olaf B. Paulson, Rigshospitalet and University of Copenhagen, will provide introductory comments and lead the discussion. Claude Wasterlain, UCLA, will summarize recent evidence on the mechanisms of transition from single seizures to status epilepticus, and experimental and clinical evidence on the most effective treatment of status epilepticus today. Sándor Beniczky, Dianalund, Denmark and Clinical Neurophysiology, Aarhus University Hospital, and Aarhus University, is the second presenter. ESI is a validated and accurate method for estimating the location of the epileptic focus. Although its clinical utility has been demonstrated, it is not used in almost 2/3 of the epilepsy centers, because it requires special expertise. This impediment can be solved by automating ESI. Lars H. Pinborg, Rigshospitale and University of Copenhagen, will speak third. It is well-known that the visual identification of structural abnormalities in pre-surgical MRI is a strong predictor of a good outcome after surgery. However, unexploited information in the high-quality presurgical MRIs could potentially inform us about post-operative histopathological diagnosis and the risk of developing cognitive and psychiatric symptoms. Olaf B. Paulson, Rigshospitalet and University of Copenhagen will conclude the panel. Single-photon emission computed tomography (SPECT) with 99mTc-HMPAO is a method to visualize the cerebral hyperperfusion during an epilepsy seizure and thus localize the epileptogenic zone and seizure propagation. Subtraction of interictal from Ictal SPECT Co-registered to MRI (SISCOM) visualizes areas with relative cerebral blood flow increase. We report predictive values for good surgical outcome, free of disabling seizures. Methodological aspects regarding seizure duration after tracer injection, as well as areas with relative flow decrease in addition to areas with flow increase are analyzed.

PANEL • TUESDAY • 4:30 PM – 6:30 PM • PRIMROSE A

Neurobiology of Circadian Rhythm and Sleep Alterations in Substance Use Disorders

Chair: Utsav Gyawali

Presenters: Rui Zhang, Mackenzie Gamble, Utsav Gyawali, Andrew Kesner

Sleep disturbances are a hallmark feature of all substance use disorders, yet the neurobiology of these sleep changes remain poorly understood. Recently, significant attention has been given to the possibility that substance use alters genes, receptors, and neurotransmitter systems involved in both sleep and reward. Our panel focuses on the translational relevance on this topic with new, unpublished data from preclinical and clinical studies examining sleep and circadian rhythm changes following repeated substance use. Our first panelist is Dr. Rui Zhang (Volkow Lab, NIDA) who will present data from patients undergoing opioid maintenance therapy that highlights a potential relationship between sleep and striatal dopamine receptors availability. Mackenzie Gamble (Ryan Logan lab, BU) will present role for the brain specific circadian transcription factor NPAS2 in opioid-induced sleep changes in humans with opioid use disorder and mice undergoing fentanyl withdrawal. We then shift focus to the use of preclinical models and the insights they can provide at a molecular and circuit/systems level. Dr. Utsav Gyawali will present evidence that cocaine abstinence is associated with sleep disruption that is linked with relapse outcomes, as well as data supporting the use of the dual orexin receptor antagonist, suvorexant, to reverse these outcomes. Finally, Dr. Andrew Kesner will discuss his laboratory's work on the sleep disrupting effects of spontaneous delta-9-tetrahydrocannabinol (THC) withdrawal. He will present work that aims to better understand the role CB1 receptors play in orchestrating sleep architecture.

PANEL • TUESDAY • 4:30 PM – 6:30 PM • PRIMROSE B

How the Gut Talks to the Brain to Influence Motivation and Reward

Chair: Sam Bacharach

Presenters: Laura Rupprecht, Nicholas DiPatrizio, Guillaume de Lartigue, Mark Rossi

The gut-brain axis is increasingly recognized as an important regulator of health and disease and represents a promising target for the treatment of both metabolic and neuropsychiatric disorders. In addition to its critical role in regulating energy homeostasis, gut-brain signaling influences mood, motivation, and learning. This panel will highlight new research examining mechanistic processes through which the gut-brain axis influences motivation for palatable foods and learning about natural rewards. Laura Rupprecht (Duke University) will present recent findings on how preferences for sugars are determined by neuropod cells in the gut. Using optogenetics inside the gut lumen, she shows that neuropod cells differentiate and transduce luminal stimuli from sweeteners and sugars to ultimately drive sugar preference. In addition to gut sensor cells, cannabinoid receptors lining the intestinal wall have been implicated in driving food preferences and motivation. Nick DiPatrizio (University of California Riverside, School of Medicine) will discuss recent studies that identify key roles for the endocannabinoid system in the gut-brain control of palatable food intake. Guillaume de Lartigue (Monell Chemical Senses Center) will present recent findings that demonstrate the existence of distinct vagal reward circuits for fat vs. sugar which increase dorsal striatal dopamine levels and promote overeating. Lastly, Mark Rossi (Rutgers University) will present his recent work on the lateral hypothalamic area (LHA). He will discuss novel findings on how the transcriptional landscape and function of distinct LHA neuron populations are modified by changing energy demands and peripherally-derived feeding hormones that are critical mediators of reward-guided behaviors. Taken together, these talks will provide a current overview of gut-brain control of reward seeking and motivation, which will pave the way for understanding new treatment avenues for disorders of motivation.

PANEL • TUESDAY • 4:30 PM - 6:30 PM • SUPERIOR

Translational Insights Into Opioid Use Disorder From Different Rodent Models of Opioid Use

Chair: Lori Knackstedt

Presenters: Devin Mueller, David Martin, Jesse Schank, Marek Schwendt

The prevalence of opioid use disorder continues to increase and is accompanied by adverse behavioral and health consequences. Humans engage in such use via multiple routes of administration and use different opioid drugs. Animal models are useful to characterize the biological underpinnings of opioid-associated behaviors. This panel describes novel brain and behavioral data from four different rodent models of opioid use, employing different routes of administration and opioids. Devin Mueller(will present data on early life adversity effects on fentanyl seeking in adolescence and adulthood across sexes. Data regarding a novel therapeutic, D-cysteine ethyl ester, on opioid respiratory depression (overdose) and fentanyl reward acquisition will also be presented. David Martin (UM-SOM) will present data from a preclinical model of intravenous fentanyl self-administration that characterizes individual differences in relapse vulnerability. In this model, discriminative stimuli promote high levels of
fentanyl seeking under reduced conflict conditions and neither sex nor individual differences with respect to sign tracking phenotypes contribute to the magnitude of relapse behavior. Jesse Schank (UGA) will present data from a rat model of concurrent access to operant self-administration of oral solutions of alcohol and oxycodone. The effects of such access on drug intake and its sensitivity to neurokinin-1 receptor antagonism will be discussed. The effects of combined drug cues and stress on the reinstatement of oxycodone seeking will also be discussed. Marek Schwendt (UF) will discuss the use of behavioral economics approaches to assess the motivation to seek intravenous oxycodone in male and female rats. The utility of such an approach for the assessment of potential therapeutics will be addressed, with data presented on the ability of systemic oxytocin to reduce the motivation to seek oxycodone in this model. The panel will conclude with a discussion of the advantages and limitations of each model.

PANEL • TUESDAY • 4:30 PM – 6:30 PM • WASATCH A

Slaloming Through Nanocolumns

Chair: Katharine Smith

Presenters: Daniel Choquet, Carolyn Brown, Katharine Smith, Kristen Harris

Choquet: Function of Nanoscale Organization of Excitatory Synapses. Super-resolution imaging and electron microscopy reveal that synaptic receptors, adhesion proteins, scaffolds, and release machinery are precisely organized in pre- and post-synaptic nanodomains. The dynamic exchange of various components between synaptic domains poses a challenge to the maintenance of this organization. This new view of synapse organization has far-reaching consequences on our interpretation on synapse function. We will focus on the nanoscale dynamics of AMPA glutamatergic receptors and its impact on synaptic plasticity.

Brown: Nanodomains within CaMKII holoenzymes. CaMKII, a key mediator of excitatory synaptic plasticity, is recently shown to control synaptic protein phase separation and nanodomain formation. Interestingly, CaMKII holoenzymes contain their very own nanodomains comprised of distinct groups of holoenzyme subunits. Here, we explore the signaling that occurs within these holoenzyme nanodomains and how this signaling, in turn, directs synaptic plasticity.

Smith: Nanoscale Organization of Inhibitory Synapses. GABAergic inhibitory synapses control neuronal excitability, firing, and plasticity. How these synapses are organized at the nanoscale, and how this organization shapes their many unique functions remain unanswered. We will describe how nanoscale inhibitory synaptic structure shapes diversity across the neuron and contributes to growth during plasticity and shrinkage in pathology.

Harris: Filling and Building Synaptic Nascent Zones. The postsynaptic density comprises regions associated with presynaptic vesicles in the active zones (AZ), and nascent zones (NZ) without vesicles. Initially, LTP recruits vesicles to the NZs, allowing nanocolumns to form with postsynaptic receptors converting NZs to AZs. Hours later, new NZs are built and LTP recovers, suggesting a mechanism for the advantage of spaced over massed learning.

PANEL • TUESDAY • 4:30 PM - 6:30 PM • WASATCH B

The Astrocyte-Neuron Interaction in Reward Circuitry: Endocannabinoid, Plasticity and Motivation

Chairs: Lanyuan Zhang, Miguel Lujan
Presenters: Jose Noriega, Janay Franklin, Eden Harder, Lanyuan Zhang

Astrocytes are the most abundant glial cells in the brain. Its functionality is heavily involved in the actuation of neuro-circuits in reward-related brain regions. This panel will discuss the latest findings on the pivotal roles of astrocytes in the hippocampus, nucleus accumbens and ventral tegmental area. Miguel Angel Lujan Perez (UMB) will give the opening remarks. Jose Noriega Prieto (UMN) will introduce the function units of astrocyte-neuron interaction and discuss how endocannabinoids distinctively modulate astrocyte-mediated neuroplasticity. Janay P. Franklin (UNC-Chapel Hill) will present her data on astrocyte-specific RNAseq for various time points of cocaine self-administration and abstinence. Eden Harder (UNC-Chapel Hill) will discuss using newly developed genetically encoded calcium indicators to study astrocytic activity with high spatial resolution. Lanyuan Zhang (UMB) will discuss how astrocytic CB1R in the ventral tegmental area regulates motivation for food reward. Overall, this panel will highlight advances in researching the information crosstalk of astrocytes and neurons utilizing multidisciplinary methods. And we will discuss how we can go beyond unveiling the physiology of astrocytes.

Wednesday, January 25, 2023

WEDNESDAY MORNING PANELS

PANEL • WEDNESDAY • 7:30 AM – 9:30 AM • BALLROOM I

From Cells to Circuits: New Frontiers in Motivation and Reward

Chairs: Melissa Sharpe, Erin Calipari

Presenters: Melissa Sharpe, Erin Calipari, James Otis, Moriel Zelikowsky

The brave new world of genetic neuroscience affords the study of neural circuits with unprecedented precision. This gives unparalleled insight into neural mechanisms governing behavior. In this panel, we present data that update current theories of reward and motivation. To start, Mel Sharpe will discuss work using optogenetics that affords new insights into the function of midbrain dopamine neurons. She will discuss new experiments using backward reward-cue conditioning that implicate the phasic dopamine prediction error as a teaching signal that facilitates the development of cognitive maps. Secondly, Erin Calipari will present data that adds to the complexity of this story by studying how dopamine acts in nucleus accumbens terminals to regulate salience during reinforcement learning, which cannot be construed as a teaching signal. Next, Jim Otis will turn to the use of two-photon calcium imaging to longitudinally track prefrontal cortical ensemble dynamics from the onset of heroin self-administration to relapse. He will discover unique neuronal ensembles that (1) differentially predict heroin seeking, (2) display day-to-day reorganization, and (3) have sexually dimorphic features. Finally, Moriel Zelikowsky will shift to social motivation and use novel assays combined with cell-type specific perturbations, unsupervised machine learning, and calcium imaging, to show that prolonged social isolation negatively impacts social motivation, communication, and mating. This panel will help broaden our understanding of the neural dynamics underlying reward and motivation, and encourage us to look beyond the expected when using new tools to examine the neuroscience of behavior.

PANEL • WEDNESDAY • 7:30 AM – 9:30 AM • MAGPIE A

Excitatory Synapse Ski for Complexity: Mechanisms of Disease and Plasticity

Chairs: Elva Diaz, Matthew Dalva
Presenters: Martin Hruska, Elva Diaz, Yael Stern-Bach, Matthew Dalva

Excitatory synapses are the fundamental connections between neurons in the brain underlying cognitive function. Defects in synapse function and plasticity are associated with a variety of neurological and neuropsychiatric disorders including autism, epilepsy, schizophrenia, and Alzheimer's disease. This panel explores molecular and cellular mechanisms of excitatory synapse structure and plasticity associated with disease states. Dr. Hruska will discuss how the synaptic nanoarchitecture underlies selective spine vulnerability in the A model of Alzheimer's disease. Dr. Diaz will discuss establishment of reserve pools of AMPA receptors necessary for synaptic plasticity and cognitive function. Dr. Stern-Bach will discuss how de-novo mutations in AMPA receptors and their auxiliary proteins, associated with developmental cognitive and motor dysfunctions, impact synaptic plasticity. Dr. Dalva will close with a discussion of the impact of disease related mutations to the NMDA receptors on the nanoscale organization of cortical spine synapses.

PANEL • WEDNESDAY • 7:30 AM – 9:30 AM • MAGPIE B

Promising Targets for Slowing Brain Aging

Chair: Natalie Ebner
Presenters: Jennifer Bizon, Perla Moreno-Castilla, Mara Mather, Teal Eich

In aging and Alzheimer's disease (AD), mnemonic functions supported by the hippocampus and executive functions supported by the prefrontal cortex are particularly vulnerable to decline. In this symposium, we present new research elucidating how these processes change in aging and potential interventions to slow down memory loss in aging. Both the hippocampus and the prefrontal cortex undergo molecular and electrophysiological alterations with age that perturb the balance between excitatory and inhibitory signaling necessary for optimal cognition. Dr. Ebner will provide introductory comments. Dr. Bizon will present data showing that electrical vagus nerve stimulation can

enhance multiple forms of prefrontal- and hippocampal-dependent learning, that are compromised in aging, and can normalize GABAergic and glutamatergic signaling in aged rats. Dr. Moreno-Castilla will present data showing that repeated theta-burst transcranial magnetic stimulation enhances memory function in aged rats with pre-treatment cognitive impairment but does not impact function in non-impaired rats. Dr. Mather will present data from a clinical trial in humans indicating that five weeks of daily sessions involving stimulating vagus nerve oscillatory activity via slow paced breathing benefited hippocampal volume in hippocampal subregions receiving strong noradrenergic input relative to an active comparison group. Dr. Eich will present data on how memorial and perceptual inhibitory processes decline differentially in aging and identify functional relationships with cortical thickness. Led by Dr. Ebner, the panel will conclude with a discussion integrating the findings in the context of current frontiers and translational impact in research on healthy aging and aging-related disease.

PANEL • WEDNESDAY • 7:30 AM – 9:30 AM • PRIMROSE A

Critical Developmental Periods for Vulnerability to Substance Use and Psychopathology

Chair: Alexandra Potter

Presenters: Alexandra Potter, Catharine Winstanley, Erik Garcia, Scott Mackey

A substantial body of evidence links substance use and stress early in life to later risk for substance dependence and other psychopathologies. However, many questions remain regarding both what are the critical periods in development in which vulnerability to these lifelong effects are highest and what are important individual differences that confer increased risk on some and not others. This symposium tackles these questions with a set of new findings drawing on both animal models of development and very large-scale longitudinal studies in humans. We will address the impact of substance exposure in utero and during adolescence and assess associations with subsequent neurocognitive functioning with a focus on adult substance use and psychosis. We will report novel animal models of drug exposure as well as the protective effects of social interactions and will report new findings on brain changes related to adolescent cannabis use that mediate subsequent use of cannabis, other drugs and psychosis symptoms. Presenters are a

multi-racial, multi-gender mix of junior and senior investigators including Scott Mackey focusing on cannabis exposure in adolescents and young adulthood, Alexi Potter describing long-term neurocognitive associations with prenatal substance exposure in humans, Catharine Winstanley describing a new rodent model of adolescent cannabis use and its impact on behavior, and Erik Garcia describing rodent investigations of early life stress and isolation leading to increased cue-induced amphetamine seeking.

PANEL • WEDNESDAY • 7:30 AM – 9:30 AM • PRIMROSE B

NMDA Receptor Signaling in Synaptic Function and Plasticity

Chair: Ulli Bayer

Presenters: Françoise Coussen-Choquet, Karen Zito, Pablo Castillo, Ulli Bayer

Higher brain functions such as learning, memory and cognition are thought to require long-term potentiation (LTP) and depression (LTD), two opposing forms of plasticity at excitatory synapses that can be triggered by high- versus low-frequency stimulation (HFS versus LFS). Both HFS-induced LTP and some forms of LFS-induced LTD are well established to require the NMDA-type glutamate receptor (NMDAR) and the Ca2+/calmodulin-dependent protein kinase II (CaMKII). Traditionally, this has been thought to require Ca2+-influx through post-synaptic NMDARs. This panel will discuss new insights into the underlying mechanisms that extend beyond the traditional view. Françoise Coussen (Université de Bordeaux) will talk about NMDAR-regulated synaptic trafficking of AMPA-type glutamate receptors. Karen Zito (University of California Davis) will describe bidirectional plasticity mechanisms that are mediated by ion flux-independent NMDAR signaling. Pablo Castillo (Albert Einstein) will describe unconventional properties of NMDAR plasticity in the hippocampus. Ulli Bayer (University of Colorado) will talk about NMDAR Ca2+-signaling that triggers Ca2+-independent CaMKII activity, including by a mechanism that is involved in the LTP impairments during normal aging.

PANEL • WEDNESDAY • 7:30 AM – 9:30 AM • SUPERIOR

The Fault in Our Stars: Astrocytes as Key Players in Addictive and Depressive Behaviors

Chairs: Anna Kruyer, Ciaran Murphy-Royal

Presenters: Anna Kruyer, Ciaran Murphy-Royal, Jacqueline-Marie Ferland, Eric Parise

Clinical data show that perturbations in astrocyte populations are common in mood and substance use disorders, though the precise role these cells play in the presentation of these psychopathologies remains unclear. Key regulators of synaptic plasticity and homeostasis, and sensors of environmental factors such as stress and drugs of abuse, astrocytes are uniquely positioned to regulate neuronal activity in response to these elements. However, how astrocytes contribute to the genesis of maladaptive behaviors in response to addictive drugs and stress is poorly understood. This panel will highlight research on the emerging role of astrocytes in addiction, stress, and depression. Dr. Kruyer will present data showing that extinction training triggers astrocyte plasticity in multiple structures within the basal ganglia to negatively modulate drug seeking. Dr. Murphy-Royal will present data showing how astrocytes influence amygdala-dependent behaviour and how these cells contribute to heightened fear generalisation following stress. Dr. Ferland will present data on astrocytic involvement in stress reactivity and decision-making deficits after high-dose adolescent THC exposure relevant to cannabis use disorder. Finally, Dr. Eric Parise will discuss the role of Htra1, an astrocyte-enriched secreted serine protease with clear sex differences in patients with major depressive disorder, in stress susceptibility and neuronal signaling using murine models. Together these presentations will provide an overview of our current understanding as to how astrocytes are recruited and play a role in stress, depression and addiction.

PANEL • WEDNESDAY • 7:30 AM – 9:30 AM • WASATCH A

Multi-Omics Analysis of Neural Plasticity During Memory Consolidation and Sleep

Chair: Graham Diering

Presenters: Iva Zovkic, Stefano Brigidi, Sara Aton, Graham Diering

Memory consolidation involves the modification neuronal connectivity and function over hours to days, including post-learning sleep, and requires the coordinated action of hundreds of molecules at the genome, transcript, and protein levels. Understanding the molecular basis for memory consolidation is accelerated by the use of multi-omics methodologies. This panel will highlight the study of memory consolidation and sleep using genomic, transcriptomic and proteomic methods.

Iva Zovkic and Stefano Brigidi will discuss how learning-induced changes in transcription are coordinated by modifying the epigenome and the combinatorial activity of inducible transcription factors (ITFs). The Zovkic lab examines how switches in histone variants H2A.Z and macroH2A1 support transcriptional programs for basal transcription vs. learning. Shifts in histones with aging and Alzheimer's disease produce sex-specific changes in transcription and memory. The Brigidi lab uses single molecule RNA imaging, transcriptional reporters and electrophysiology to uncover distinctive patterns of ITF expression in single neurons together with in vivo imaging to track the activity of ITFs in the days post-learning.

Sara Aton and Graham Diering will describe how neurons and synapses are negatively affected by sleep deprivation (SD). The Aton lab uses Targeted Recombination in activated populations (TRAP) to selectively label and monitor engram associated hippocampal neurons, showing that reactivation of engram neurons is disrupted by post-learning SD. Spatial profiling is used to identify changes in transcript and protein levels after learning and subsequent sleep or SD. The Diering lab uses sub-cellular fractionation and proteomics to identify the molecular basis for the negative effects of SD on synapse functions in developing and adult mice. SD has a profound impact on the developing synapse proteins and phosphorylations, while mice gain resilience to the effects of SD with maturation.

PANEL • WEDNESDAY • 7:30 AM – 9:30 AM • WASATCH B

Ovarian Hormone Regulation of Motivation and Emotion: Implications for Psychiatric Disease

Chair: Elizabeth Lucas

Presenters: Lillian Brady, Laura Been, Elizabeth Lucas, Mohammed Milad

Epidemiology data suggest that ovarian hormones contribute to sex differences in the prevalence and presentation of common mental illnesses such as addiction, depression, anxiety, and post-traumatic stress. In this panel, we will discuss the neurobiological mechanisms driving ovarian hormone regulation of motivation and emotion. Dr. Lillian Brady will provide data supporting estradiol regulation of dopamine neurotransmission through nicotinic acetylcholine receptors in the nucleus accumbens core in mice. Her data highlight the effects of non-classical sex steroid hormone receptor signaling that underlies reward learning and motivation associated with substance use disorder. Dr. Laura Been will describe long-term alterations in nucleus accumbens plasticity associated with altered affective states in the hormone-simulated pseudopregnancy model of postpartum estrogen withdrawal in mice. Her ongoing work combines pharmacology, electrochemical recordings, and behavior testing to investigate the mechanism of this neuroplasticity and link it to affective changes. Dr. Elizabeth Lucas will present work linking ovarian hormone regulation of inhibitory microcircuits in the basolateral amygdala with changes in anxiety-like behavior across the reproductive cycle in mice. Contrary to current models, her work suggests that amygdala inhibition promotes, rather than inhibits, avoidance behavior. Dr. Mohammed Milad will close our panel with functional MRI data that reveal a significant impact of exogenous estradiol on distributed neural networks associated with emotional learning and memory consolidation in healthy women. He will discuss the potential use of estradiol administration as an adjunct to current exposure-based therapies for anxiety and fear-based disorders. Together, our data showcase the diverse actions of ovarian hormones on neural circuits underlying behavioral states relevant for psychiatric disease and provide mechanistic insights for pharmacological interventions.

WEDNESDAY AFTERNOON PANELS

PANEL • WEDNESDAY • 4:30 PM – 6:30 PM • BALLROOM I

Defining and Manipulating Neural Circuits That Govern Reward-Related Behaviors

Chairs: Michael Stefanik, Michael Scofield

Presenters: Michael Stefanik, Michael Scofield, Kathleen Bryant, Alexa Zimbelman

Until recently, the heterogeneous nature and complexity of neural pathways contributing to reward-related behaviors has largely remained an enigma. Advances in tools to dissect and manipulate specific neural circuits and defined cell types in the brain has provided a novel opportunity to understand the pathways that contribute to these behaviors, especially when they go awry. This panel will focus on studies that combine animal models of substance abuse with cutting-edge optogenetic, chemogenetic, and viral tracing tools to gain a better understating of the circuits that contribute to reward-related behaviors. Michael Stefanik (North Central College) will present data using retrograde viral tracing tools to determine pathway-specific alterations involved in the incubation of oxycodone craving. Michael Scofield (MUSC) will present data using intersectional anterograde transsynaptic neuron to neuron and anterograde axo-astro neuron to astroglia viral vector technologies to elucidate circuit specific aspects of the neuronal and astroglial biology underlying drug seeking. Kathleen Bryant's (Drexel) research focuses on the role of the ventral hippocampus (vHPC) during the regulation of reward seeking. She will present findings using in-vivo electrophysiology to indicate that chronic low-dose ethanol exposure alters vHPC encoding and closed-loop optogenetic inhibition of vHPC projections can be used to drive inflexible reward-seeking behavior. Alexa Zimbelman (Iowa) will conclude the session with data utilizing closed-loop activity-controlled optogenetic procedures to delineate the neural pathways from the infralimbic cortex to either the nucleus accumbens shell or amygdala involved in the extinction of cocaine seeking. This panel will provide perspectives on the utilization of diverse circuit-specific tools in rodents to explore the underpinnings of substance use disorders.

PANEL • WEDNESDAY • 4:30 PM – 6:30 PM • MAGPIE A

Diet, Exercise, and Gut Metabolism: Convergent Molecular Pathways Affecting Brain Function and Behavior

Chairs: Philipp Mews, Marcelo Wood

Presenters: Drew Kiraly, Marcelo Wood, Philipp Mews, Steven Fordahl

This panel will showcase rapidly developing research on the role of peripheral factors as regulators of brain and behavior in neuropsychiatric disease. Exercise, nutrition, and gut metabolism converge on complex communication pathways along metabolic and epigenetic routes to influence brain tissue at the molecular and transcriptional levels. However, little is known about the impact of these metabolic stimuli on memory-related behaviors in health and disease. Drew Kiraly (Wake Forest) will show that manipulations of the gut microbiome and its metabolites alter rewarding properties of drugs of abuse and transcriptomic control in the brain. He will discuss how manipulations of the gut microbiome alter reinstatement of fentanyl seeking in a rodent model of drug relapse, implicating epigenome regulation by gut metabolites. Marcelo Wood (UC Irvine) will show that a 'molecular memory window' is responsible for maintaining the cognitive benefits of exercise, driven by a molecular mechanism at the interface of epigenetics and acetyl-CoA metabolism that supports memory formation during this 'window' under inadequate learning conditions. Philipp Mews (Mount Sinai) will discuss how neural gene expression and drug-related memory are 'fueled' by chromatin-localized production of acetyl-CoA. He will show how blocking a key acetyl-CoA synthetase enzyme over a narrow time window can selectively disrupt specific memories and prevent relapse-related behaviors. Steven Fordahl (UNC Greensboro) will show how a diet with low, medium, or high levels of saturated fat alters dopamine release and uptake kinetics in the nucleus accumbens. His talk will highlight how proinflammatory cytokines alter dopamine terminal function, and how increasing dietary fat intake may enhance microglial activity. Together, the panel will provide a cutting-edge view of how interactions of peripheral systems with the brain epigenome alter neurobiological plasticity in translationally relevant behavioral models.

PANEL • WEDNESDAY • 4:30 PM - 6:30 PM • MAGPIE B

Novel Functions for proSAAS in the Regulation of Feeding, Body Weight, Drug Abuse, and Neurodegenerative Disease

Chairs: Daniel Morgan, Lloyd Fricker

Presenters: Daniel Morgan, Erin Bobeck, Amanda Fakira, Iris Lindberg

Neuropeptides are a large and diverse class of intercellular signaling molecules in the brain and make up a family consisting of hundreds of known neuropeptides that signal through G protein-coupled receptors to modulate a wide range of biological processes. ProSAAS was originally identified as an endogenous inhibitor of prohormone convertase 1/3, an enzyme responsible for the processing of hormone and neuropeptide precursors. ProSAAS is widely expressed in brain and neuroendocrine tissues and is processed into secreted peptides including big-SAAS, little-SAAS, PEN, and bigLEN. These peptides are among the most abundant neuropeptides in brain, suggesting that they perform important functions. In 2013, bigLEN was found to bind and activate GPR171, a hypothalamic GPCR involved in feeding behavior. Several years later, GPR83, was identified as the GPCR for PEN peptide. In this timely panel symposium, we will discuss recent progress and advances in our understanding of proSAAS signaling pathways in body weight regulation, chronic pain, and mood regulation. Lloyd Fricker (Einstein College of Medicine) will provide a short introduction on the history of proSAAS, the peptides derived from this precursor and the deorphanized GPCRs for proSAAS-derived peptides. Daniel Morgan (Marshall Univ) will present recent work demonstrating that proSAAS knock-out mice exhibit resistance to high fat diet-induced obesity. Erin Bobeck (Utah State Univ) will describe research from her lab demonstrating sex differences in the role of GPR171 in inflammatory and chemotherapy-evoked neuropathic pain. Amanda Fakira (Rowan Univ) will discuss her recent work on the role of GPR83 in opioid-induced antinociception and reward. Finally, Iris Lindberg (Univ. of Maryland) will present recent progress on the neuroprotective role of proSAAS in various neurodegenerative diseases such as Parkinson's, Alzheimer's and ALS.

PANEL • WEDNESDAY • 4:30 PM – 6:30 PM • PRIMROSE A

Pleasure Despite Pain: Interventions and Mechanisms That Promote Resilient Adaptation to Chronic Pain
Chair: Patrick Finan
Presenters: Patrick Finan, Fadel Zeidan, Anne Baker

Pain was traditionally conceptualized as a biobehavioral phenomenon that principally interacted with negative valence systems, for example as antecedent or sequelae to negative affective states. However, research has begun to reveal the dialectical interactions between pain and reward, which have been observed across multiple levels of analysis, including experimental, observational, and interventional paradigms. Although behavioral and biological reward deficits appear to be associated with risk for chronic pain, interventions that augment reward functioning may ameliorate that risk. The proposed panel will address several important questions regarding reward function in the face of chronic pain. Dr. Patrick Finan will begin by providing an overview of the literature on pain and reward and present behavioral and fMRI data from a recently completed mechanistic clinical trial in which patients with rheumatoid arthritis were trained to practice a brief, novel positive emotion-enhancing meditation (called Savoring) in the context of noxious stimuli. Dr. Fadel Zeidan will then present his work on the neuroimaging of mindful breathing and analgesia, offering insights on the degree to which emotion-agnostic mindfulness practices engage reward versus non-reward pathways. Finally, Dr. Anne Baker will present novel data addressing individual differences in the association of pain and reward, with a focus on sex/gender differences. Individual presentations will be brief to allow for an audience participatory discussion of clinical and research agendas that can move this growing area of pain research forward.

PANEL • WEDNESDAY • 4:30 PM – 6:30 PM • PRIMROSE B

Stress Adaptation Versus Maladaptation: Implications for Diseases Susceptibility and Resilience

Chair: Jason Radley

Presenters: Debra Bangasser, Jason Radley, Erica Glasper, Mathias Schmidt

Animal studies have implicated alterations in behavioral, metabolic, and transcriptional changes in stress-related psychiatric diseases. However, the neural bases thought to represent antecedents for pathology may also be the same as those enlisted to promote stress adaptation. Thus, dissociating adaptive from maladaptive responses remains a crucial consideration in the translation to human disease susceptibility and resilience. In this symposium we will highlight different perspectives of neurobiological mechanisms underlying responses to stress followed by a discussion of how these may lend insight into understanding human susceptibility and resilience. First, Dr. Debra Bangasser (Georgia State University) will discuss how exposure to brief, early postnatal scarcity in rats has “inoculating” effects in adulthood by reducing impulsivity in males and risky decision making in both sexes. She will present new data revealing key cell-specific transcriptomic changes in the prefrontal cortex that promote these cognitive features of resilience. Dr. Jason Radley (University of Iowa) will highlight new evidence that a prefrontal–midbrain circuit promotes broad stress buffering effects on behavioral and endocrine responses in rats, albeit only under the more adverse conditions. Dr. Erica Glasper (The Ohio State University College of Medicine) will discuss stress-related mechanisms that may underlie social vigilance and social anxiety behaviors following early life adversity in a biparental mouse species. Finally, Dr. Mathias Schmidt (Max Planck Institute of Psychiatry) will present data how early life adversity in interaction with the genetic risk factor Fkbp5 can have maladaptive as well as adaptive molecular, structural, and behavioral consequences in an age and sex-specific manner.

PANEL • WEDNESDAY • 4:30 PM – 6:30 PM • SUPERIOR

Serotonergic Roles in Addiction and Motivation

Chair: Thomas Jhou

Presenters: Thomas Jhou, Catharine Winstanley, Christina Merritt

Dopaminergic systems play major well-recognized roles in addictions and motivated decision-making. However, serotonergic systems are also involved in these behaviors but in ways that have been harder to discern, in part due to the large number of serotonin receptors involved. Notably, serotonin 2 class receptors may be particularly important in decision-making in regards to addiction and its treatment. For example, new data from the Jhou lab has elucidated a serotonin 2C role in cocaine's delayed aversive "crash", with these receptors activating GABAergic neurons in the rostromedial tegmental nucleus to inhibit dopamine neurons. The strength of this inhibition is stronger in "high-crasher" individuals, giving rise to particularly strong aversive responses to cocaine along with apparent protection against drug-seeking. In addition to roles in aversion, these receptors also play roles in the risk-reward decisions that may be dysregulated in addiction. New studies from the Winstanley lab show that antagonism of 5-HT2C receptors within the orbitofrontal cortex can ameliorate the ability of win-paired cues to drive risky decision making, which may be of relevance to the ability of psychedelic treatment to improve cognitive flexibility. However, despite the importance of these receptors in behavioral regulation, previous agonist-based treatments for addictions have suffered from off-target effects that could be ameliorated by the use of drugs that are more selective and modulatory in nature. Toward this end, new work from Dr. Christina Merritt shows first-in-class positive allosteric modulators (PAMs) of the 5-HT2A receptor (5-HT2AR) and 5-HT2CR showing improved selectivity over orthosteric modulators of the 5-HT2R family, thereby creating new opportunities to optimize 5-HT2R signaling in disorders marked by cortical dysfunction, including substance use disorders.

PANEL • WEDNESDAY • 4:30 PM – 6:30 PM • WASATCH A

Chronic Opioid Induced Neuroadaptations: Focus on Hyperalgesia and Individual Differences

Chair: Renata Marchette

Presenters: Elyssa Margolis, David Barker, Renata Marchette

Many key questions remain regarding the underlying neurobiology that generates persistent negative affect that increases the likelihood of the development of chronic pain and substance use disorder. Conceptualizing population variability as individual differences in these conditions may facilitate the identification of mechanistic biological heterogeneity that contributes to apparent behavioral variability. In this session we examine in-depth behavioral phenotyping of individual differences with molecular and circuit-level analyses to provide a big picture/holistic view of critical biological conditions prior to opioid abuse and the neuroadaptations caused by opioid exposure and may predict differences in treatment outcomes.

Dr. Renata Marchette (Chair) will give a brief panel introduction to the advantages of considering individual differences in pain and opioid research.

Dr. Elyssa Margolis will describe circuit specific adaptations of MOR and DOR function following consumption of drugs of abuse, chronic pain, or stress. She will contrast changes in VTA circuits to those observed in lateral habenula circuits.

Dr. David Barker will show how broad behavioral phenotyping can reveal specific phenotypes indicative of future susceptibility to heightened opioid intake and the role that stress plays in modifying opioid susceptibility.

Dr. Renata Marchette will share an in-depth behavioral analysis of escalation of drug intake, opioid seeking and taking despite punishment, motivation, and hyperalgesia in opioid dependent and non-dependent mice. She will also show new data on how vulnerability to hyperalgesia predicts addiction-like behaviors.

Together these talks highlight how careful attention to individual differences can improve experimental design, increase the power of interpretation, and lead to more informative behavioral and mechanistic models.

PANEL • WEDNESDAY • 4:30 PM – 6:30 PM • WASATCH B

Naturalistic Neuroimaging and Psychiatry: Where Do We Go From Here?

Chair: Oliver Robinson

Presenters: Emily Finn, Tamara Vanderwal, Peter Kirk, Gaurav Patel

Our theories concerning the neurobiological bases of psychiatric illness have been built on the foundation of tightly-controlled neuroimaging paradigms using largely simple, static stimuli. Yet, whether or not patterns of brain activity generalize to more naturalistic settings in the real world is unclear. In recent years, we have therefore started to see extension of neuroimaging into the richer, more complex domain of 'movie fMRI'. This presents an opportunity to test whether prior findings generalize to more naturalistic settings. It also, critically, enables us to overcome some of the increasingly documented limitations of standard neuroimaging paradigms in understanding individual differences in psychiatric symptoms. For instance, movie fMRI can improve measurement reliability, reduce artifacts, improve participant engagement while also constituting a more sensitive probe of the functions (e.g. emotions, social processing) that contribute to psychiatric illness. This panel will provide the audience with an overview of the rich possibilities of movie fMRI, highlight recent developments, and discuss ways in which we can use these methods to better understand the broad transdiagnostic spectrum of psychiatric illness. Specifically, Emily Finn will provide an introduction to movie fMRI and provide examples of how it can be used to understand individual differences (e.g. in psychiatric symptoms), Tamara Vanderwal will discuss the advantages of this approach for studying child psychiatric disorders, Peter Kirk will discuss the advantages of movie fMRI in understanding anxiety, and Gaurav Patel will discuss the application of this approach to social perception in Schizophrenia. Oliver Robinson will provide introductory comments and lead discussion of the presentations.

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